PART III : APPLICATION OF THREE-COMPONENT PALLADIUM-CATALYSED CASCADE REACTION OF DIKETOPIPERAZINE AND 1,4-BENZODIAZEPINE DERIVATIVES

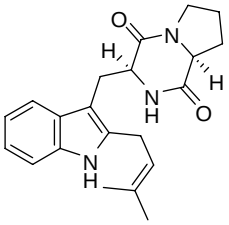
INTRODUCTION

The exploration of privileged structures in drug discovery has been very useful in medicinal chemistry. Privileged structures are molecular building blocks capable of binding to a range of enzymes/receptors with high affinity. (Evans *et al*., 1988; Nicolaou *et al*., 2000) The exploitation of these molecules assists the medicinal chemist in discovering biologically active compounds across a broad range of therapeutic areas on a reasonable time scale.

Heterocyclic privileged structures include 1,4-benzodiazepine-2-one and 1,4-benzodiazepine-2,5-dione derivatives. (Evans *et al*., 1988; De Sarro *et al*., 1997; Ramdas *et al*., 1999; Stevens *et al*., 1996; Bhalay *et al*., 1997; Evans *et al*., 2001; Wyatt *et al*., 2001; Keating *et al*., 1996; Hulme *et al*., 1998; Mayer *et al*., 1996) and diketopiperazine derivatives. (Horton *et al*., 2002; Baures *et al*., 1997; Wang *et al*., 2000; Hayashi *et al*., 2000; López-Rodríguez *et al*., 2001; Li *et al*., 2002; Prakash *et al*., 2002; Wang *et al*., 2002; Slee *et al*., 2003)

The diketopiperazines are the smallest cyclic peptides and their derivatives are found in many biologically interesting natural products. More recently, they have gained importance in drug discovery, as inhibitors of various enzymes, including topoisomerases and collagenase-1, as well as being bradykinin antagonists and opioid receptor agonists and antagonists. (Acharya *et al*., 2001) Diketopiperazines also showed high affinity for 5-HT_{1A} receptors (López-Rodríguez *et al*., 2001; López-Rodríguez *et al*., 2001), neuroprotective activity (Prakash *et al*., 2002) and as

inhibitors of plasminogen activator inhibitor-1 (PAI-1)(Wang *et al*., 2002). Tryprostatin B (**215**) and demethoxyfumitremorgin C (**216**) analogues are fungal inhibitors of mammalian cell cycle progression at the G_2/M transition. (Wang *et al*., 2000) Phenylahistin (**217**) exhibited cytotoxicity against a wide variety of tumour cell lines. (Hayashi *et al*., 2000)



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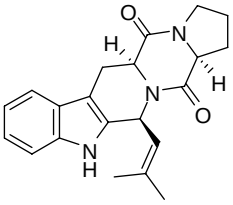

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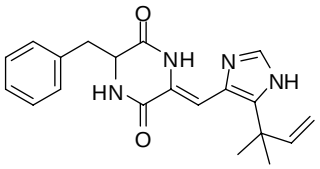


217

1,4-Benzodiazepin-2-ones are the archetypal privileged structure, and they show a range of activities that includes anticonvulsant activity, neurokinin antagonists, opioid receptor agonists, cholecystokinin receptor (CCK) A and B antagonists, oxytocin antagonists, HIV transactivator-Tat antagonists, HIV reverse transcriptase inhibitors and potassium channel blockers. (Evans *et al*., 1988; De Sarro *et al*., 1997; Ramdas *et al*., 1999; Stevens *et al*., 1996; Bhalay *et al*., 1997; Evans *et al*., 2001) 1,4-Benzodiazepin-2,5-diones possess a similar range of biological activities that includes anticonvulsant, anxiolytic, and antitumor properties, as well as being CCK receptor, opiate receptor and platelet glycoprotein IIb-IIIa antagonists. (Keating *et al*., 1996; Hulme *et al*., 1998; Mayer *et al*., 1996)

Hence, the synthesis of unusual diketopiperazines is interesting in order to study their biological activity together with their reactivity and selectivity in synthetic processes. The key step of my syntheses is a three-component Pd-catalysed cascade reaction which is a 'one pot' multi-step process. (Zimmer *et al*., 2000; Heumann *et al*., 1997) In my studies the three-component system comprises of *N*-allenyl diketopiperazines, 1,4-benzodiazepin-2-ones and 1,4-benzodiazepin-2,5-diones derivatives, aryl halides and *N*- or *C*-nucleophiles. The catalytic cascade process is more convenient, effective and produces less waste.

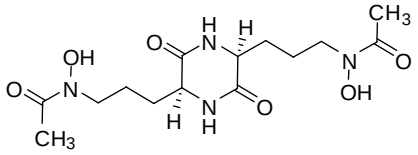
LITERATURE REVIEWS

Diketopiperazine and 1,4-Benzodiazepine Derivatives: Synthesis and Activity

Diketopiperazine Derivatives

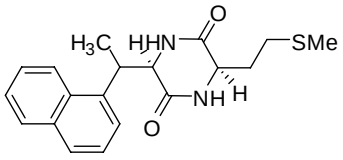
Biological activities

In 1968, Atkin and Neilands isolated rhodotorulic acid (**218**), a diketopiperazine dihydroxamic acid, from a red yeast, *Rhodotorula pilimanae*. Rhodotorulic acid showed potent growth-factor inhibition activity in assays with *Arthrobactor* species.



Rhodotorulic acid, **218**

In 1987, Shimazaki *et al*. found a new class of platelet-activating factor (PAF) inhibitors. The diketopiperazine (**219**), showed activity of the same order as or rather superior to that of the natural product FR900452 (**220**) which was isolated from a metabolite of a *Streptomyces*.



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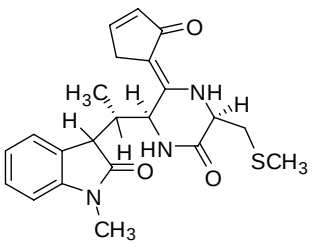
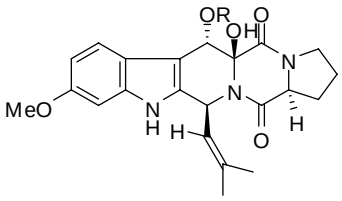


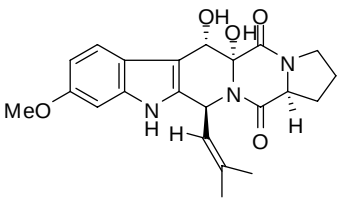
FR900452, **220**

Cyclotryprostatins A-D (**221**-**224**), isolated from the secondary metabolites of *Aspergillus fumigatus* by Osada and co-workers in 1997, are new inhibitors of the mammalian cell cycle.

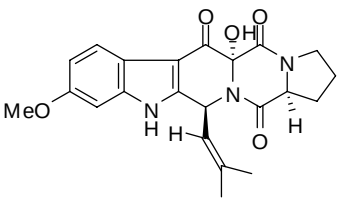


R = H , Cyclotryprostatin A, **221**

R = CH_3 , Cyclotryprostatin B, **222**

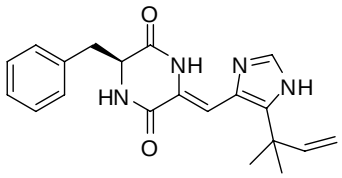


Cyclotryprostatin C, **223**



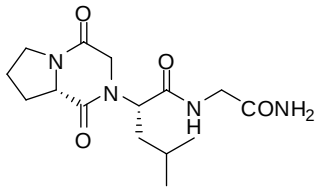
Cyclotryprostatin D, **224**

In the same year, Kanoh *et al*. reported the isolation of (-)-phenylahistin (**217**) from *Aspergillus ustus* and this compound showed cytotoxic and cell cycle inhibitory activities.



(-)-Phenylahistin, **217**

Baures *et al*. designed and synthesized diketopiperazine peptidomimetics of *L*-prolyl-*L*-leucylglycinamide and studied their dopamine receptor modulating activity. Compounds **225** and **226** were agonists at the [^{3}H]spiroperidol/*N*-propylnorapomerphine D_2 receptor.



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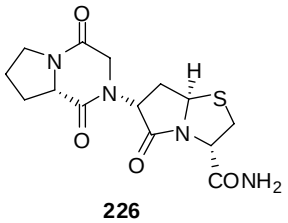
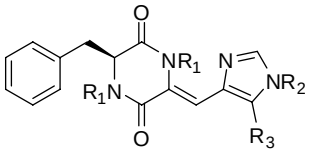


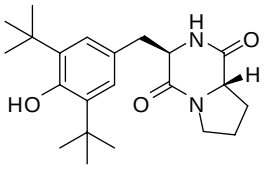
226

In 1999, Kanoh *et al*. found that (-)-phenylahistin derivatives (**227**) exhibited anti-microtubule activity by forming a rigid uniplanar pseudo three-ring structure due to intermolecule hydrogen bonding between NH in diketopiperazine ring and nitrogen atom in imidazole ring.



227

In 2002, Kozikowski and co-workers reported the synthesis of diketopiperazine derivatives (**228** and **229**) with neuroprotective properties.



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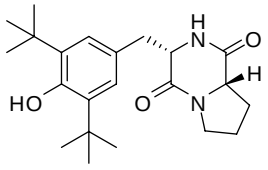
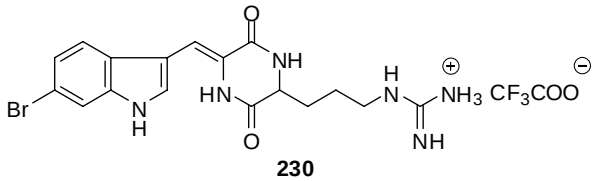


229

In 2004, Bohlin *et al*. isolated barettin (cyclo[(6-bromo-8-entryptophan)arginine], **230**) and 8,9-dihydrobarettin (cyclo[(6-bromotryptophan) arginine], **231**) from the marine sponge *Geodia barrette*. These compounds showed potent antifouling activity.



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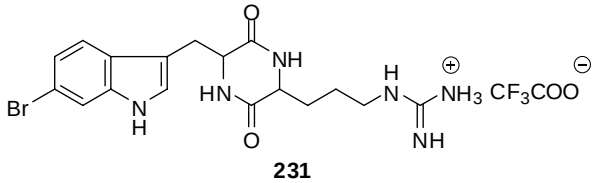
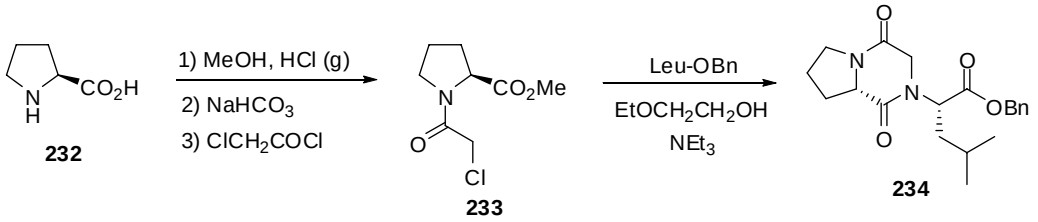


231

Synthetic method

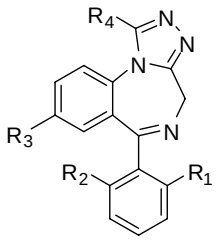
Synthesis of diketopiperazine analogues was accomplished starting from *L*-proline (**232**) *via* the *N*-chloroacetyl derivative (**233**) (**Scheme 47**) (Baures *et al*., 1997, Pandey *et al*., 2000)



Scheme 47

1,4-Benzodiazepine Derivatives

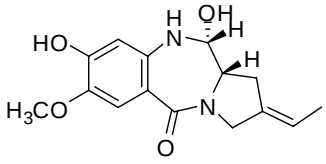
In 1971, a series of 6-phenyl-4*H*-s-triazolo[4,3-α][1,4]benzodiazepine derivatives (**235**) was prepared by Hester and co-workers. These compounds showed high central nervous system (CNS) depressant activity with low concomitant toxicity.



235

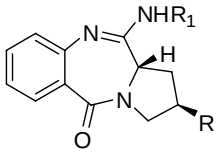
In 1988, Hurley *et al*. described the relationship of DNA alkylation and sequence specificity of the biological activity of natural and synthetic pyrrolo[1,4]benzodiazepine derivatives. These compounds were evaluated for in vitro cytotoxic activity against B16 melanoma cells, for potency in vivo in $B6D2F_1$ mice (LD_{50}) and for antitumor activity (ILS_{max}) against P-388 leukemia cells. They found that all pyrrolo[1,4]benzodiazepine derivatives especially tomaymycin (**236**) showed

potent cytotoxic activity against B16 melanoma cell line and all of them did not showed antitumor activity against P-388 cell line .



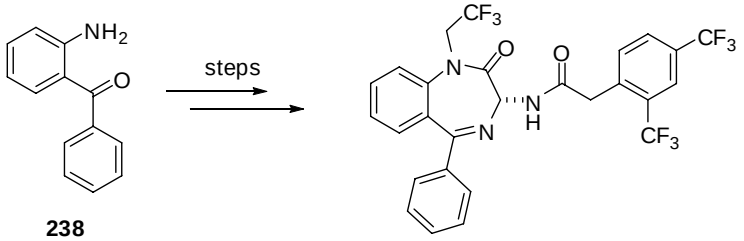
236

In 1996, Foloppe and co-workers synthesized the pyrrolo[2,1-c][1,4]-benzodiazepine N10-C11 amidine derivatives (**237**). They found that an N10-C11 amidine moiety can play an important role in the non-covalent DNA binding of pyrrolo[2,1-c][1,4]-benzodiazepine dilactams.



237

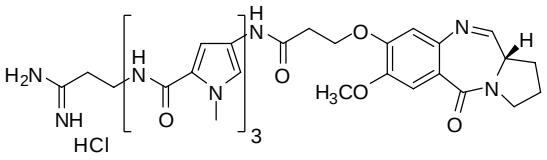
In 1997, Selnick *et al*. synthesized L-768,673, ((*R*)-2-(2,4-trifluoromethyl)-*N*-[2-oxo-5-phenyl-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1*H*-benzo[e][1,4]diazepin-3-yl] acetamide (**239**), and related benzo[1,4]diazepin-3-yl acetamide derivatives from 2-amino benzophenone (**238**)(**Scheme 48**). Compound **239** is an orally active, potent and selective potassium channel (I_{Ks}) blocking agent that exerts significant class III activity in vivo and does not cause after depolarization in vitro.



238 **239**, L-768,673

Scheme 48

In 1998, Baraldi *et al*. synthesized a pyrrolo[2,1-c][1,4]benzodiazepine-distamycin hybrid (**240**) which is related to the naturally occurring anthramycin and distamycin A (**241**). Compound **240** exhibited antiproliferative activity with an IC_{50} value of 0.2 μM. Later, Baraldi and co-workers reported pyrrolo[2,1-c][1,4]benzodiazepine-distamycin hybrids containing one to four pyrrole units to study structure-activity relationships.



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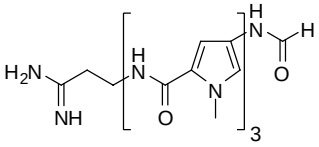
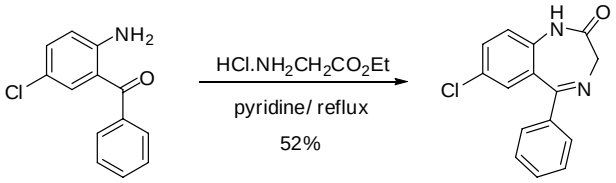


241, Distamycin A

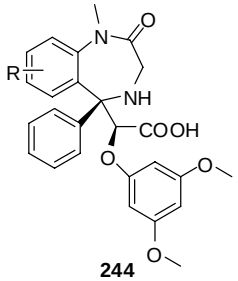
The synthesis of 1,4-benzodiazepine (**243**), reported by Boruah *et al*, 1988, was achieved by treatment of 2-amino-5-chlorobenzophenone (**242**) with glycine ester hydrochloride under reflux in dry pyridine (**Scheme 49**).



242 **243**

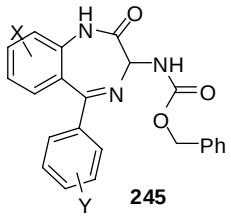
Scheme 49

In 2004, Bolli and co-workers reported the synthesis of benzo[1,4]diazepin-2-one derivatives (**244**) as well as their in vitro and in vivo structure-activity relationship as endothelin receptor antagonists.



244

In 2006, Carter *et al*. synthesized 1,4-benzodiazepine analogues (**245-250**) containing 3-amide/urea derivatives, as inhibitors of respiratory syncytial virus (RSV). They found that o-methoxybenzamide containing electron-withdrawing group gave both excellent in activity and pharmacokinetic properties. Substitution around the bicyclic template gave no improvement in activity. Moreover, alkylation of either the ring or substituent amide NH groups also led to a loss of activity.



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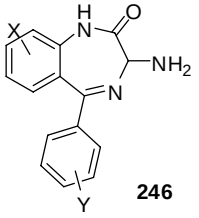

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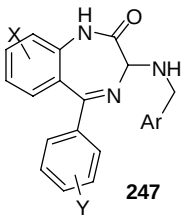

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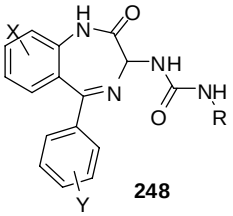

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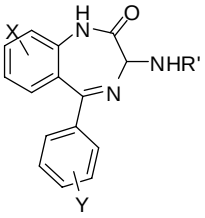
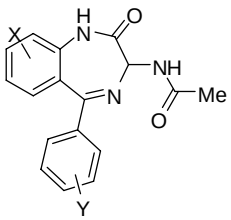


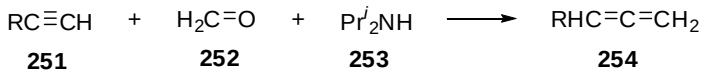
R' = RCO or RSO_2

249



250

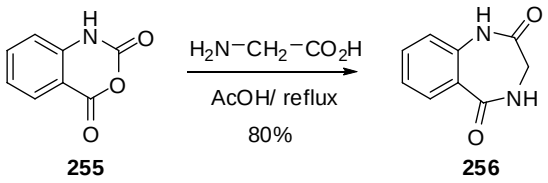
Homologation of terminal alkyne to the corresponding allenes in good yield was investigated and reported by Searles *et al*. Alk-1-yne was reacted with formaldehyde and diisopropylamine in the presence of catalytic cuprous bromide in 1,4-dioxane as shown in **Scheme 50**. The mechanism proposed involves an intermediate hydrido-cuprate species derived from a Mannich base-cuprous bromide π–complex. (Searles *et al*., 1984)



251 **252** **253** **254**

Scheme 50

The synthesis of 3H-1(*H*),4(*H*)-benzodiazepin-2,5-diones (**256**) was accomplished in good yield by reaction of isatoic anhydride (**255**) and α-amino acids in glacial acetic acid under reflux as shown in **Scheme 51**. (Mohiuddin *et al*., 1985)

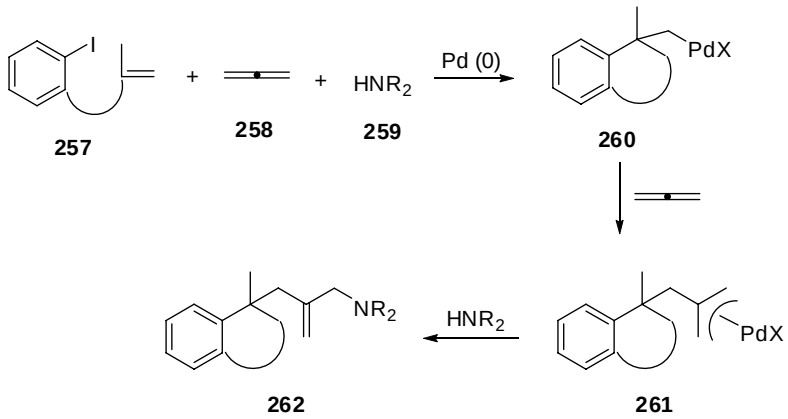


255 **256**

Scheme 51

Palladium-Catalysed Cascade Reaction

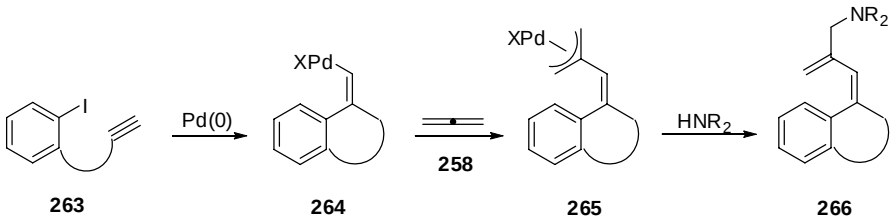
In 1996, Grigg *et al*. reported a palladium-catalysed process employing allenes and involving cyclisation forming 5- and 6-membered rings (**Scheme 52**).



257 **258** **259** **260** **262** **261**

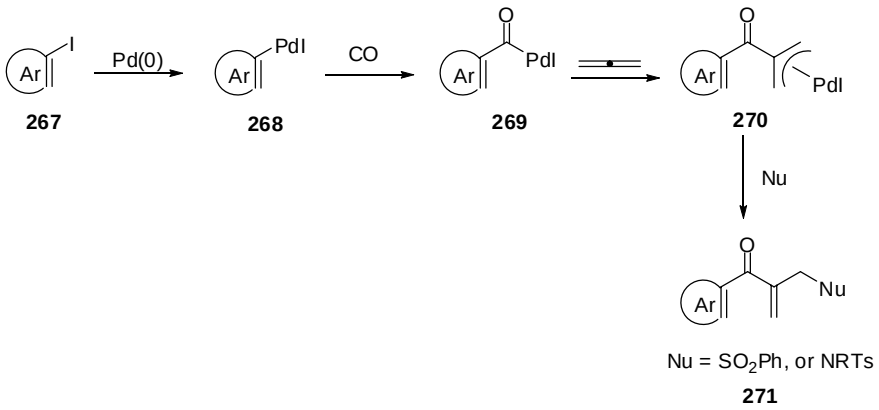
Scheme 52

In the same year, Grigg and Savic described termolecular queuing cascades involving palladium catalysed cyclisation onto proximate alkynes followed by allene insertion and capture of the resulting π–allylpalladium (II) species by secondary amines (**Scheme 53**).



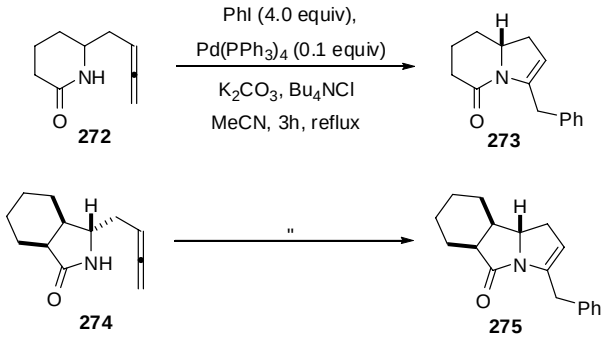
Scheme 53

Grigg and co-workers also reported a palladium catalysed tetramolecular cascade processes incorporating allene and carbon monoxide in 1997. This cascade process involves formation of three new bonds (**Scheme 54**).



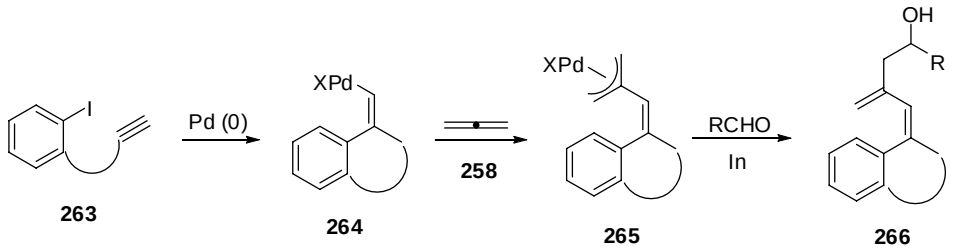
Scheme 54

In addition, Karstens *et al*. reported the palladium-catalyzed coupling/cyclization reactions of allene-substituted lactams and aryl iodides (**Scheme 55**).



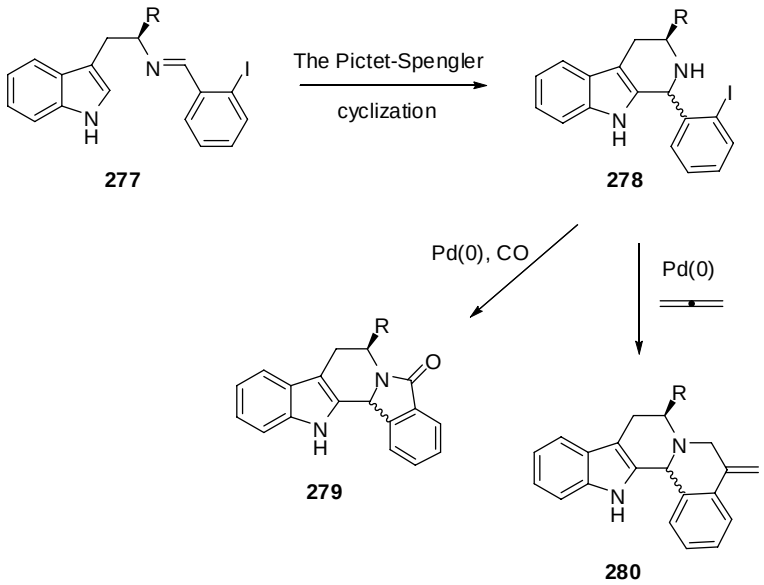
Scheme 55

In 2000, Anwar and co-workers reported palladium/indium-catalysed cyclisation-Barbier-type allylation cascades. The cascade process, involving cyclisation of aryl halides onto alkynes, allene insertion, transmetallation of the resulting π–allylpalladium species with indium and addition to an aldehyde, provided heterocyclic and carbocyclic dienes (**Scheme 56**).



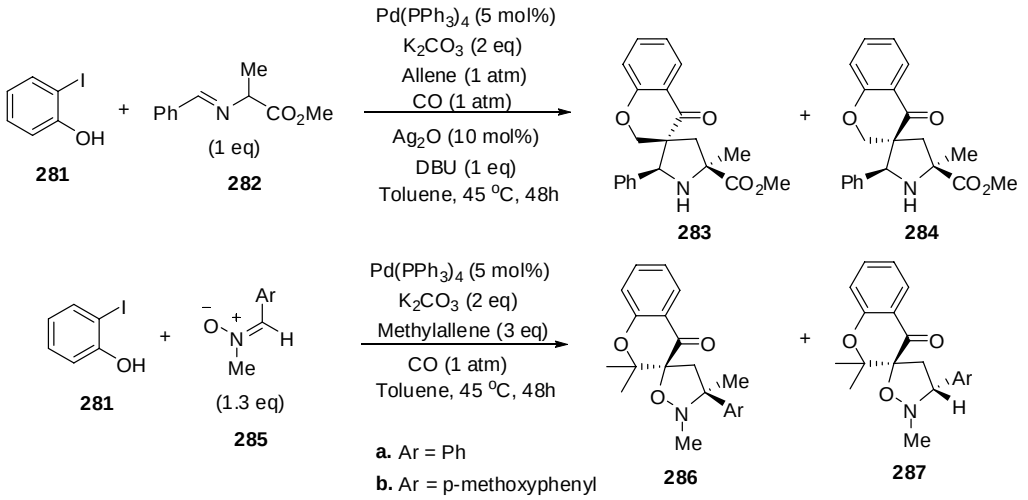
Scheme 56

In the same year, Grigg *et al*. reported the combination of the Pictet-Spengler reaction with Pd-catalysed reactions with allene and carbon monoxide to provide complex heterocycles with good regio- and stereo-selectivity (**Schemes 57**).



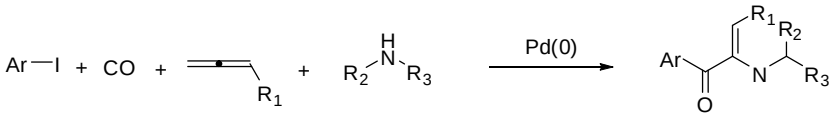
Scheme 57

In addition, Grigg's group reported cascade reactions incorporating palladium-catalysed termolecular queuing processes and 1,3-dipolar cycloaddition reactions to provide a range of structurally diverse pyrrolidine, isoxazolidine, isoxazoline, dihydropyran and pyrazoline derivatives (**Scheme 58**).

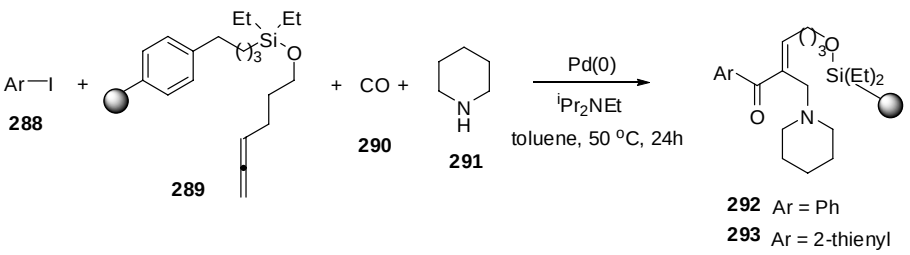


Scheme 58

Moreover, Grigg *et al*. studied the palladium-catalysed four-component cascade reaction comprising aryl iodides, CO, polymer supported allene and amines. The complex heterocycles were formed by three new bonds in good yield and excellent purity after cleavage. (**Scheme 59**)

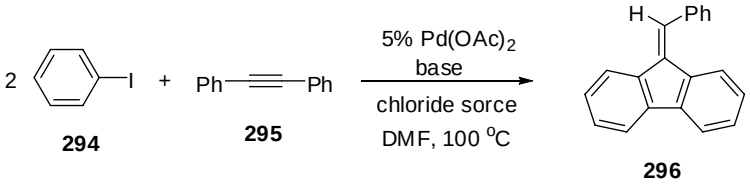


For example:



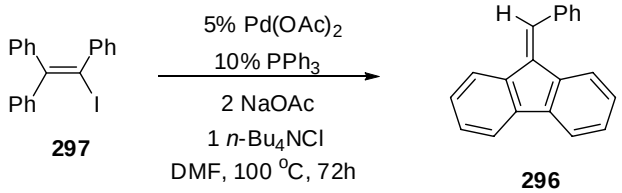
Scheme 59

In 2001, Larock and Tian synthesized 9-alkylidene-9*H*-fluorenes (**296**) by palladium-catalyzed cascade reaction of aryl halides (**294**) and 1-aryl-1-alkynes (**295**)(**Scheme 60**). The products are highly dependent on the base employed. The process proceeds by an unusual cascade migration/coupling process involving a novel rearrangement of a vinylic palladium intermediate to an arylpalladium species. On the basis of this proposed mechanism, the same product was prepared from vinylic iodide (**297**) (**Schemes 60** and **61**).



294 **295** **296**

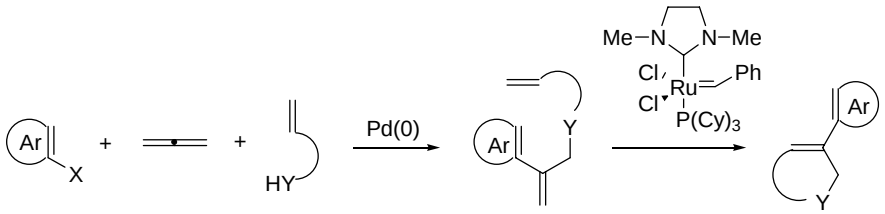
Scheme 60



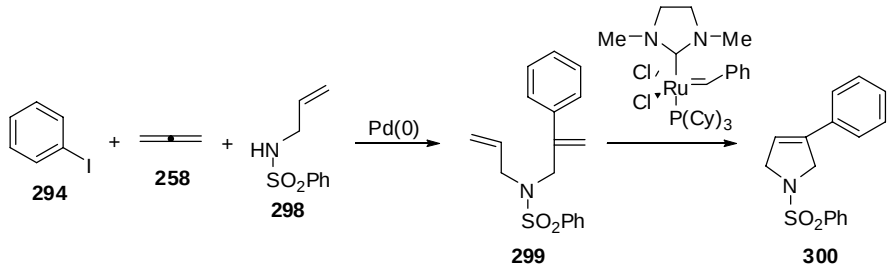
297 **296**

Scheme 61

In the same year, Dondas and co-workers synthesized heterocycles via sequential Pd/Ru-catalysed allene insertion-nucleophile incorporation followed by ruthenium-catalysed ring-closing metathesis (**Scheme 62**).

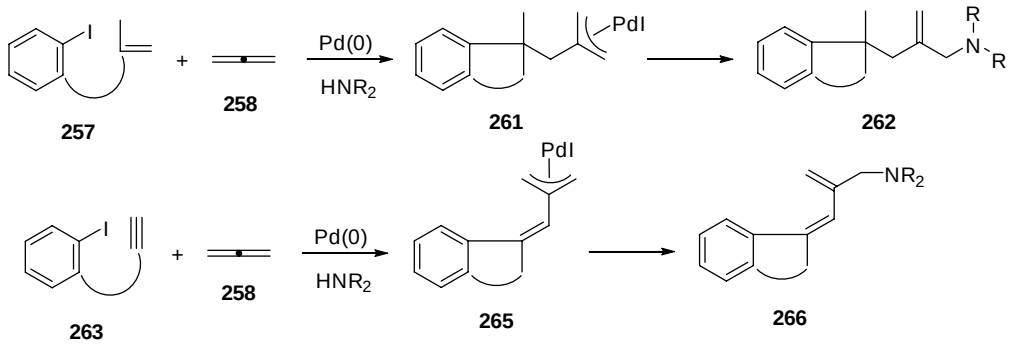


For example:



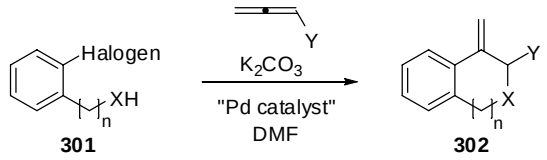
Scheme 62

In 2002, Grigg *et al* reported a palladium-catalysed termolecular queuing cascade reaction involving cyclization onto a proximate alkene or alkyne followed by allene insertion and capture of the resulting π-allyl palladium (II) species by secondary amines (**Scheme 63**).



Scheme 63

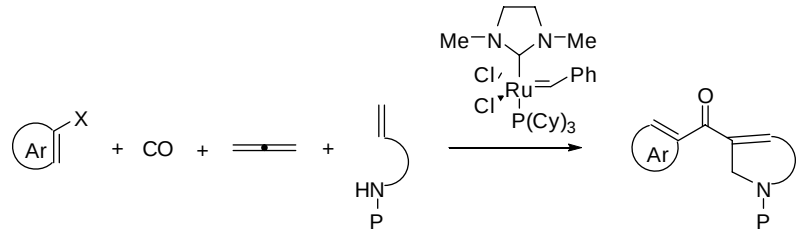
In 2005, Inamoto *et al*. developed a highly regioselective synthesis of heterocycles via palladium-catalyzed annulation of heteroatom-substituted allenes. Additionally, unprecedented S_N2' reaction of alkyl metal reagents occurred at the exomethylene position of annulated products and several alkyl moieties were introduced in good to high yields. (**Scheme 64**)



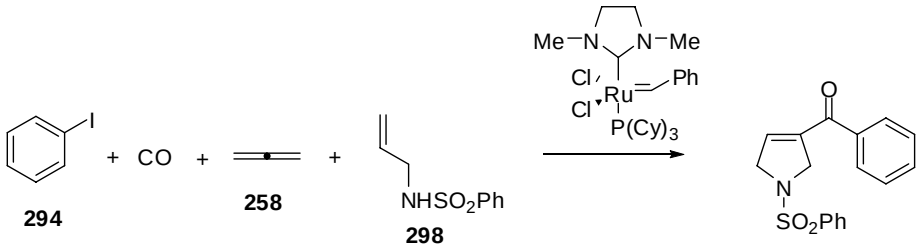
n = 0, 1
x = O, N(CO_2Et), NTs Y = OBn, N(Ts)Bn

Scheme 64

In the same year, Grigg and co-workers described a palladium-catalysed four-component process involving carbon monoxide, allene and aryl/heteroaryl iodides generating (π-allyl) palladium species, which were intercepted by alkene tethered nitrogen nucleophiles to give 1,6- and 1,7-dienones. Subsequent ring closing metathesis provided 5- and 6-membered *N*-heterocyclic enones (**Scheme 65**).



For example:



294 **258** **298** **303**

Scheme 65

MATERIALS AND METHODS

Materials

Instrumentations

Melting points (m.p.) were determined on a Reichert hot-stage apparatus at the School of Chemistry, University of Leeds, United Kingdom and are incorrected.

Infrared (IR) spectra were obtained on a Phillips PU 9706 spectrophotometer at the School of Chemistry, University of Leeds, United Kingdom.

Low resolution mass spectral data were determined on a Micromass LCT (TOF MS ES+) instrument at the School of Chemistry, University of Leeds, United Kingdom. High resolution mass spectral data was obtained using reserpine as an internal reference ($C_{33}H_{40}N_2O_9$ (M+H), 609.2812) at EPSRC National Mass Spectrometry Service Centre, Department of Chemistry, University of Wales Swansea, United Kingdom.

Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker DPX 300 or Bruker DRX 500 or Bruker Avance 500 LC or Bruker Avance 500 instrument at the School of Chemistry, University of Leeds, United Kingdom. Chemical shifts (δ) are expressed in parts per million (ppm) relative to internal tetramethylsilane (TMS) and coupling constants (J) are given in Hertz (Hz). Chemical shifts (δ) are given in parts per million (ppm) downfield from tetramethylsilane (TMS) as internal standard. Coupling constants (J) are given in Hertz (Hz). Unless otherwise specified deuterochloroform ($CDCl_3$) was used as a solvent. The following abbreviations are used: s = singlet, d = doublet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, br s = broad singlet, dd = doublet of doublet, dt = doublet of triplet, td = triplet of doublet, qd = quartet of doublet, ddd = doublet of doublet of doublet.

Microanalyses were performed using a Carbo Erba MOD1106 instrument. Analytical HPLC were obtained on a LUNA 10μ C18(2), 250×4.6 mm modules reverse phase column and a uv (254 nm) detector and optical rotation were recorded on an AA 1000 Polarimeter at the School of Chemistry, University of Leeds, United Kingdom.

Chromatographic systems

Thin-layer chromatography (TLC) on aluminum sheets with silica gel 60 F_{254} was used routinely for monitoring reaction progress. The chromatograms were visualized under ultraviolet light (254 nm).

Flash column chromatography was performed with silica gel (Davisil, 60 Å, 35-60 mesh).

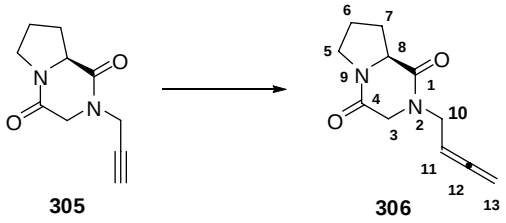
Chemical reagents

All reagents and solvents were used as received from Merck, Fluka and Aldrich Chemical.

Methods

Synthesis of *N*-allenyl diketopiperazine derivatives

2-Buta-2,3-dienyl-hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione, (-)-306



A mixture of terminal alkyne **(-)-305** (2 g, 10.4 mmol), paraformaldehyde (780 mg, 26 mmol), diisopropylamine (2.92 mL, 26.0 mmol) and copper (I) bromide (746 mg, 5.2 mmol) in 1,4-dioxane (70 mL) was stirred and refluxed under argon atmosphere for 4 h. The reaction mixture was filtered and the solids washed several times with hot CH_2Cl_2. The filtrate was evaporated under reduced pressure, the residue was dissolved in CH_2Cl_2 (150 mL) and washed with 10% aqueous ammonia solution (3×100 mL) and brine (150 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under vacuo. The residue was purified by flash column chromatography eluting with 2% MeOH-CH_2Cl_2 to give the product **306**as a pale yellow solid (1.64 g, 76%) which crystallized from isopropanol-*n*-pentane as colourless prisms. Mp: 81-82 °C.

^{1}H NMR (500 MHz, $CDCl_3$, δ): 5.10 (quint, J=6.5 Hz, 1H, C*H*-11), 4.85 (m, 2H, C*H*$_2$-13), 4.14 (d, J_{AB}=16.6 Hz, 1H, C*H*-3), 3.96-4.09 (m, 3H, C*H*-8, C*H*$_2$-10), 3.84 (d, J_{AB}=16.6 Hz, 1H, C*H*-3), 3.63 (m, 1H, C*H*-5), 3.54 (m, 1H, C*H*-5), 2.40 (m, 1H, C*H*-7), 2.06 (m, 2H, C*H*-6, C*H*-7), 1.91 (m, 1H, C*H*-6).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 210.30 (C), 167.49 (CO), 163.63 (CO), 85.66 (CH), 77.69 (CH_2), 59.43 (CH), 51.64 (CH_2), 45.66 (CH_2), 44.86 (CH_2), 29.28 (CH_2), 23.06 (CH_2).

IR (ν_{max}, cm^{-1}): 2984, 2975, 2885 (CH_2), 1955, 1667, 1643 (C=O), 1457, 1343, 1301, 1262, 1228 (C=C).

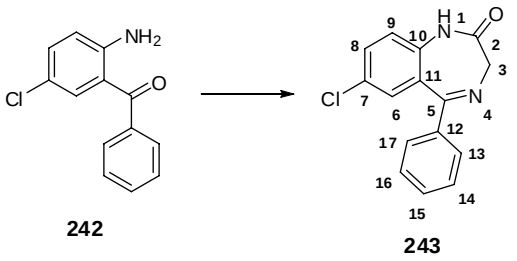
ESI-MS (*m/z*, % rel. intensity): 207 (100, $[M+H]^+$).

Optical rotation: $[\alpha]_D^{22}$ = -112 (*c* 1.0, $CHCl_3$).

Anal. calcd for $C_{11}H_{14}N_2O_2$: C 64.06, H 6.84, N 13.58. Found: C 64.00, H 6.80, N 13.50.

Synthesis of *N*-allenyl -5-phenyl-1,4-benzodiazepin-2-one derivatives

7-Chloro-5-phenyl-1,3-dihydro-benzo[e][1,4] diazepin-2-one (243)



242 **243**

A mixture of 2-amino-5-chlorobenzophenone (**242**) (9.85 g, 42.51 mmol) and glycine ethyl ester hydrochloride (13.86 g, 99.27 mmol) was refluxed in dry pyridine (200 mL) for 24 h. Then pyridine was removed and the residue was dissolved in Et_2O. The solution was washed with water (3×200 mL). The organic layer was separated, and 1 M NaOH added to the aqueous layer to bring the solution to pH 12. After that the aqueous layer was extracted twice more with Et_2O and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The residue was purified by flash column chromatography with 40% EtOAc-hexane to afford the desired product **243** (4.00 g, 93 %, 43 %conversion) as pale yellow prisms and the starting material (5.55 g) as yellow plates. Mp: 216–217 °C (Sternbach *et al.*, 1961, 216–217 °C).

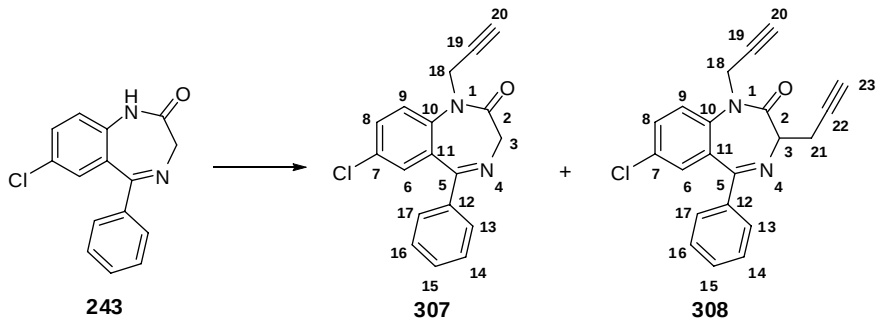
^{1}H-NMR (500 MHz, $CHCl_3$, *δ*): 9.56 (br s, 1H, N*H*), 7.54–7.39 (m, 6H, Ar*H*), 7.30 (d, *J*=2.3 Hz, 1H, Ar*H*-6), 7.14 (d, *J*=8.7 Hz, 1H, Ar*H*-9), 4.33 (br s, 2H, CH_2-3).

^{13}C-NMR (125 MHz, $CHCl_3$, *δ*): 172.12 (C), 169.91 (C), 138.79 (C), 137.37 (C), 131.87 (CH), 130.73 (CH), 130.66 (C), 129.60 (2×CH), 128.87 (C), 128.55 (C), 128.42 (2×CH), 122.76 (CH), 56.64 (CH_2).

IR (ν_{max}, cm^{-1}): 3208 (NH), 3056 (CH-aromatic), 2947 (CH_2), 1689 (C=O), 1609, 1578, 1481, 1323, 1232 (C=C).

ESI-MS (*m/z*, % rel. intensity): 271 (100, $[M+H]^+$).

7-Chloro-5-phenyl-1-prop-2-ynyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one (307)



Method A

7-Chloro-5-phenyl-1,3-dihydro-benzo[*e*][1,4]diazepin-2-one **(243)** (3.53 g, 13.04 mmol) in *N,N*-dimethylformamide (30 mL) was added dropwise to a stirred mixture of sodium hydride (0.469 g, 19.56 mmol, 60 % suspension in mineral oil) in *N,N*-dimethylformamide (70 mL) at 0 ^oC under a N_2 atmosphere. The reaction mixture was stirred continuously at this temperature for 0.5 h. When propargyl bromide (2.18 mL, 19.56 mmol, 80 % solution in toluene) was slowly added to the cooled solution. The mixture was stirred for 14 h and slowly allowed to warm to room temperature. Water (150 mL) was added, and the mixture left to stir for 0.5 h. Ethyl acetate (3×100 mL) was added and the organic layer was washed with water (2×100 mL), dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated under vacuo. The residue was purified by flash column chromatography eluting with 25% EtOAc-hexane to afford the desired product **307** (2.4268 g, 60 %) as colourless prisms and dialkylated product **308** (1.0037 g, 22%) as colourless needles.

Method B

7-Chloro-5-phenyl-1,3-dihydro-benzo[*e*][1,4]diazepin-2-one **(243)** (3.00 g, 11.64 mmol) in *N,N*-dimethylformamide (25 mL) was added dropwise to a stirred

solution of sodium hydride (0.419 g, 17.46 mmol, 60 % suspension in mineral oil) in *N,N*-dimethylformamide (60 mL) at 0 ^{o}C under N_2 atmosphere. The reaction mixture was stirred continuously at this temperature for 0.5 h. Then propargyl bromide (1.43 mL, 12.80 mmol, 80 % solution in toluene) was slowly added over 5 minutes to the cooled solution. The mixture was stirred for 3 h and slowly allowed to warm to room temperature. Water (150 mL) was then added, and the mixture left to stir for 0.5 h. Ethyl acetate (3×100 mL) was added and the organic layer was washed with water (2×100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The residue was purified by flash column chromatography eluting with 25% EtOAc-hexane to afford the desired product **307** (3.011 g, 88 %) as colourless prisms. M.p.: 143-144 °C.

^{1}H-NMR (300 MHz, $CHCl_3$, δ): 7.65–7.39 (m, 7H, Ar*H*), 7.30 (d, *J*=2.3Hz, 1H, Ar*H*-6), 4.86 (d, J_{AB}=10.8 Hz, 1H, C*H*H-3), 4.67 (dd, *J*=17.5, 2.5 Hz, 1H, C*H*H-18), 4.51 (dd, *J*=17.5, 2.5 Hz, 1H, CH*H*-18), 3.81 (*d*, J_{AB}=10.8 Hz, 1H, CH*H*-3), 2.29 (t, *J*=2.5 Hz, 1H, H-20).

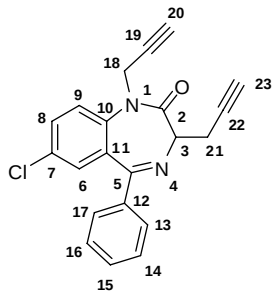
^{13}C-NMR (63 MHz, $CHCl_3$, δ): 169.61 (C), 169.25 (C), 141.25 (C), 138.61 (C), 131.94 (CH), 131.16 (CH), 131.08 (C), 130.42 (C), 130.35 (CH), 129.89 (2×CH), 128.84 (2×CH), 123.17 (CH), 79.03 (C), 73.31 (CH), 57.18 (CH_2), 37.18 (CH_2).

IR (ν_{max}, cm^{-1}): 3286 (CH-alkyne), 3056 (CH-aromatic), 2972, 2851(CH_2), 1687 (C=O), 1609, 1482, 1405, 1322, 1266 (C=C).

ESI-MS (*m/z*, % rel. intensity): 309 (100, $[M+H]^+$).

Anal. calcd for $C_{18}H_{13}{}^{35}ClN_2O$: C, 70.02; H, 4.24; Cl, 11.48; N, 9.07. Found: C, 69.8; H, 4.40; Cl, 11.45; N, 9.05.

7-Chloro-5-phenyl-1,3-di-prop-2-ynyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one (308)



308

M.p.: 164-165 °C.

^{1}H-NMR (500 MHz, $CHCl_3$, δ): 7.60 (m, 3H, Ar*H*), 7.56 (dd, *J*=2.3, 8.8 Hz, 1H, Ar*H*-8), 7.48 (m, 1H, Ar*H*), 7.41 (m, 2H, Ar*H*), 7.33 (d, *J*=2.3 Hz, 1H, Ar*H*-6), 4.64 (d, *J*=2.3 Hz, 2H, CH_2-18), 3.83 (t, *J*=7.0 Hz, 1H, *H*-3), 3.15 (dd, *J*=2.6 and 7.0 Hz, 2H, CH_2-21), 2.24 (t, *J*=2.3 Hz, 1H, *H*-20), 2.00 (t, *J*=2.6 Hz, 1H, *H*-23).

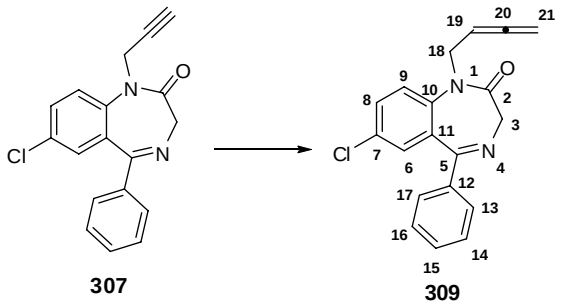
^{13}C-NMR (75 MHz, $CHCl_3$, δ): 168.73 (C), 168.19 (C), 140.56 (C), 138.33 (C), 132.12 (CH), 131.52 (C), 131.25 (CH), 130.69 (C), 130.30 (CH), 130.08 (2×CH), 128.86 (2×CH), 123.60 (CH), 82.12 (C), 78.86 (C), 73.39 (C), 70.20 (C), 63.24 (CH), 37.41 (CH_2), 22.44 (CH_2).

IR (ν_{max}, cm^{-1}): 3286 (CH-alkyne), 3057 (CH-aromatic), 2948 (CH_2), 1688 (C=O), 1607, 1480, 1406, 1323, 1264 (C=C).

ESI-MS (*m/z*, % rel. intensity): 347 (100, $[M+H]^+$).

Anal. calcd for $C_{21}H_{15}{}^{35}ClN_2O$: C, 72.73; H, 4.36; Cl, 10.22; N, 8.08. Found: C, 72.65; H, 4.60; Cl, 10.30; N, 8.10.

1-Buta-2,3-dienyl-7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one (309)



307 **309**

A mixture of 7-chloro-5-phenyl-1-prop-2-ynyl-1,3-dihydro-benzo[*e*][1,4] diazepin-2-one (**307**) (2.43 g, 7.86 mmol), paraformaldehyde (1.71 g, 19.65 mmol), diisopropyl amine (2.2 mL, 15.72 mmol) and copper (I) bromide (0.564 g, 3.93 mmol) was dissolved in 1,4-dioxane (80 mL) and refluxed under a N_2 atmosphere for 14 h. The dioxane was removed under vacuo, the residue dissolved in CH_2Cl_2 (150 mL) and extracted with aqueous ammonia (3×100 mL) and brine (100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated under vacuo. The residue was purified by flash column chromatography eluting with 30% EtOAc-hexane to yield the product **309** (1.56 g, 75 %) as colourless prisms. Mp: 133-134 °C.

^{1}H-NMR (500 MHz, $CHCl_3$, δ): 7.59 (m, 2H, Ar*H*), 7.40–7.51 (m, 5H, Ar*H*), 7.27 (d, *J*=1.9 Hz, 1H, Ar*H*-6), 5.25 (m, 1H, *H*-19), 4.83 (d, J_{AB}=10.5 Hz, 1H, C*H*H-3), 4.72–4.80 (m, 2H, CH_2-21), 4.47 (m, 2H, CH_2-18), 3.78 (d, J_{AB}=10.5 Hz, 1H, CH*H*-3).

^{13}C-NMR (125 MHz, $CHCl_3$, δ): 208.71 (C), 169.09 (C), 168.70 (C), 141.58 (C), 138.25 (C), 131.37 (CH), 130.81 (C), 130.69 (CH), 129.87 (CH), 129.56 (C), 129.45 (2×CH), 128.43 (2×CH), 123.21 (CH), 86.91 (CH), 77.46 (CH_2), 57.03 (CH_2), 46.36 (CH_2).

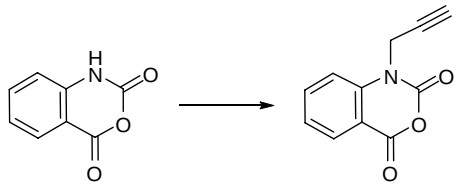
IR (ν_{max}, cm^{-1}): 3054 (CH-aromatic), 2974, 2939 (CH_2), 1682 (C=O), 1608, 1481, 1405, 1322, 1269 (C=C).

ESI-MS (*m/z*, % rel. intensity): 323 (100, $[M+H]^+$).

Anal. calcd for $C_{19}H_{15}{}^{35}ClN_2O$: C, 70.70; H, 4.68; Cl, 10.98; N, 8.68. Found: C, 70.95; H, 4.9; Cl, 11.25; N, 8.75.

Synthesis of *N*-allenyl-1,4-benzodiazepin-2,5-dione derivatives

1-Prop-2-ynyl-2H-3,1-benzoxazine-2,4(1H)-dione (310)



255 **310**

Isatoic anhydride (**255**) (5.00 g, 30.6 mmol) in *N*,*N*-dimethylformamide (25 mL) was added over 15 minutes to a stirred solution of sodium hydride (1.35 g, 33.6 mmol, 60 % suspension in mineral oil) in *N*,*N*-dimethylformamide (50 mL) at 0 °C under a N_2 atmosphere and the mixture was stirred for 0.5 h at this temperature. Propargyl bromide (6.14 mL, 55.1 mmol, 80 % solution in toluene) was then added over 10 minutes and the mixture left to stir for 6 h at room temperature. Water (150 mL) was slowly added to the reaction mixture, and the aqueous mixture was extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated under vacuo. The residue was crystallised from dichloromethane-Et_2O to provide the product **310** (5.21 g, 84 %) as pale yellow needles. Mp: 139-140 °C (Vincent, 1971, m.p. 140-143 °C).

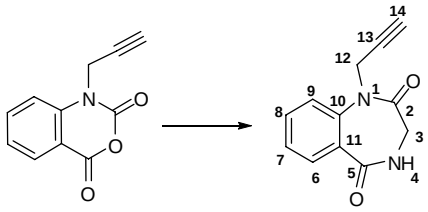
^{1}H-NMR (500 MHz, $CHCl_3$, δ): 8.19 (dd, *J*=7.9 Hz, 1H, Ar*H*), 7.81 (td, *J*=1.3 and 7.9 Hz, 1H, Ar*H*), 7.35 (m, 2H, Ar*H*), 4.87 (d, *J*=2.4 Hz, 2H, N-CH_2-C≡C*H*), 2.37 (t, *J*=2.4 Hz, 1H, CH_2-C≡C*H*).

^{13}C-NMR (75 MHz, $CHCl_3$, δ): 157.94 (CO), 147.39 (CO), 140.36 (C), 137.33 (CH), 130.92 (CH), 124.52 (CH), 114.44 (CH), 111.82 (C), 75.94 (C), 74.42 (CH), 34.61 (CH_2).

IR (ν_{max}, cm^{-1}): 2989, 2917 (CH_2), 1781, 1722 (C=O), 1607, 1478 (C=C).

ESI-MS (*m/z*, % rel. intensity): 202 (100, $[M+H]^+$).

1-Prop-2-ynyl-3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione (311)



310 **311**

A mixture of 1-prop-2-ynyl-2*H*-3,1-benzoxazine-2,4(1*H*)-dione **(310)** (5.60 g, 27.7 mmol) and glycine (4.16 g, 55.4 mmol) was dissolved in glacial acetic acid (42 mL) and refluxed for 4 h. The reaction mixture was neutralised with 1 M NaOH to pH 4.5 and the aqueous phase extracted with dichloromethane (3×100 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated under vacuum. The residue was purified by flash column chromatography eluting with 50% EtOAc-hexane to give the product **311** (5.42 g, 91 %) as pale yellow prisms. Mp: 208-209 °C.

^{1}H-NMR (500 MHz, $CHCl_3$, δ): 7.91 (dd, *J*=1.1 and 6.9 Hz, 1H, Ar*H*), 7.58-7.65 (m, 2H, Ar*H*), 7.37 (t, *J*=7.3 Hz, 1H, ArH), 6.96 (br s, 1H, N*H*), 4.80 (d,

J_{AB}=17.1 Hz, 1H, C*H*H-12), 4.28 (d, J_{AB}=17.1 Hz, 1H, CH*H*-12), 3.86 (m, 2H, CH_2-3), 2.35 (t, *J*=2.4 Hz, 1H, C*H*-14).

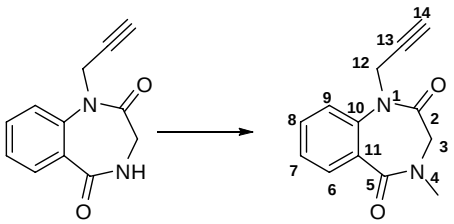
^{13}C-NMR (125 MHz, $CHCl_3$, δ): 169.19 (CO), 168.98 (CO), 140.54 (C), 133.25 (CH), 131.26 (CH), 127.88 (C), 126.87 (CH), 121.69 (CH), 79.21 (CH), 73.20 (C), 45.43 (CH_2), 38.44 (CH_2).

IR (ν_{max}, cm^{-1}): 3293 (NH), 3071 (CH-aromatic), 2926 (CH_2), 1666 (C=O), 1603, 1470, 1396, 1217 (C=C).

ESI-MS (*m/z*, % rel. intensity): 215 (100, $[M+H]^+$).

Anal. calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 66.9; H, 4.85; N, 13.25.

4-Methyl-1-prop-2-ynyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (312)



1-Prop-2-ynyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione **(311)** (5.78 g, 26.90 mmol) in *N*,*N*-dimethylformamide (30 mL) was added over 15 minutes to a stirred solution of sodium hydride (1.18 g, 29.59 mmol, 60 % suspension in mineral oil) in *N*,*N*-dimethylformamide (70 mL) at 0 °C under a N_2 atmosphere and the mixture was stirred for 0.5 h at this temperature. Methyl iodide (2.01 mL, 32.28 mmol) was added over 10 minutes and the mixture was left to stir for 1.5 h at room temperature. Water (200 mL) was slowly added to the reaction mixture, and the aqueous mixture was extracted with dichloromethane (3×100 mL). The combined

organic layers were dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated under vacuo. The residue was purified by flash column chromatography eluting with 50% EtOAc-hexane to afford the product **312** (4.45 g, 72 %) as colourless needles. Mp: 134-135 °C.

^{1}H-NMR (500 MHz, $CHCl_3$, δ): 7.87 (dd, *J*=1.2, 7.8 Hz, 1H, Ar*H*-6), 7.54–7.61 (m, 2H, Ar*H*-8,9), 7.33 (t, *J*=7.4 Hz, 1H, Ar*H*-7), 4.78 (dd, *J*=2.4 and 17.4 Hz, 1H, C*H*H-12), 4.26 (dd, *J*=2.4 and 17.4 Hz, 1H, CH*H*-12), 4.10 (d, J_{AB}=14.7 Hz, 1H, C*H*H-3), 3.72 (d, J_{AB}=14.7 Hz, 1H, CH*H*-3), 3.28 (s, 3H, CH_3-15), 2.35 (t, *J*=2.4 Hz, 1H, C*H*-14).

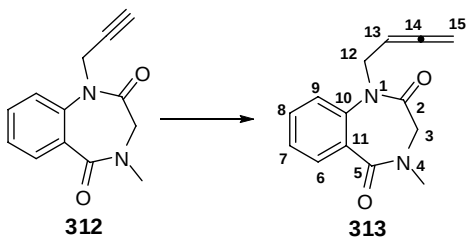
^{13}C-NMR (75 MHz, $CHCl_3$, δ): 168.16 (CO), 167.52 (CO), 140.12 (C), 132.62 (CH), 131.24 (CH), 129.19 (C), 126.62 (CH), 121.09 (CH), 79.20 (C), 73.25 (CH), 53.34 (CH_2), 37.87 (CH_2), 36.46 (CH_2).

IR (ν_{max}, cm^{-1}): 3060, 3016 (CH-aromatic), 2936 (CH_2), 1686, 1644 (C=O), 1602, 1482, 1397, 1233 (C=C).

ESI-MS (*m/z*, % rel. intensity): 229 (100, $[M+H]^+$).

Anal. calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.2; H, 5.75; N, 11.7.

1-Buta-2,3-dienyl-4-methyl-3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione (313)



A mixture of 4-methyl-1-prop-2-ynyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**312**) (4.44 g, 20.67 mmol), paraformaldehyde (4.49 g, 51.68 mmol), diisopropyl amine (3.02 mL, 41.31 mmol) and copper (I) bromide (1.48 g, 10.34 mmol) was dissolved in 1,4-dioxane (150 mL) and refluxed under N_2 atmosphere for 16 h. Then the dioxane was removed under vacuo. The residue was dissolved in dichloromethane (150 mL) and extracted with aqueous ammonia (3×100 mL) and brine (100 mL). After that the organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The residue was then purified by flash column chromatography eluting with 1% MeOH-CH_2Cl_2 to give the allene product (**313**) (4.19 g, 89 %) as a pale yellow solid. Mp: 98-99 °C.

^{1}H-NMR (500 MHz, $CHCl_3$, δ): 7.86 (dd, *J*=1.4 and 7.6 Hz, 1H, Ar*H*-6), 7.50 (td, *J*=1.4 and 8.3 Hz, 1H, Ar*H*-8), 7.35 (d, *J*=8.3 Hz, 1H, Ar*H*-9), 7.30 (t, *J*=7.6 Hz, 1H, Ar*H*-7), 5.31 (m, 1H, C*H*-13), 4.79-4.85 (m, 2H, CH_2-15), 4.49–4.54 (m, 1H, C*H*H-12), 4.34-4.39 (m, 1H, CH*H*-12), 4.08 (d, J_{AB}=14.5 Hz, 1H, C*H*H-3), 3.67 (d, J_{AB}=14.5 Hz, 1H, C*H*H-3), 3.27 (s, 3H, CH_3-16).

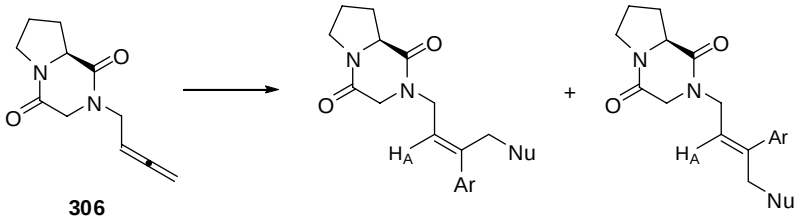
^{13}C-NMR (125 MHz, $CHCl_3$, δ): 206.76 (C), 166.01 (CO), 165.65 (CO), 138.61 (C), 130.38 (CH), 129.16 (CH), 127.77 (C), 124.32 (CH), 119.69 (CH), 85.39 (CH), 76.18 (CH_2), 51.50 (CH_2), 44.93 (CH_2), 34.34 (CH_3).

IR (ν_{max}, cm^{-1}): 3061 (CH-aromatic), 2933 (CH_2), 1678, 1646 (C=O), 1602, 1481, 1398, 1231 (C=C).

ESI-MS (*m/z*, % rel. intensity): 243 (100, $[M+H]^+$).

Anal. calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.20; H, 5.75; N, 11.70.

Palladium-Catalysed Cascade Reactions of *N*-Allenyl Diketopiperazine Derivative



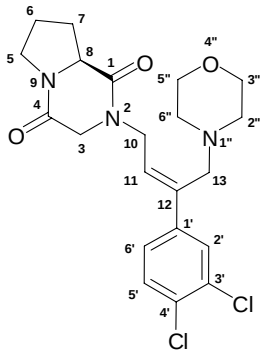
306 **314**, *Z*-isomer **315**, *E*-isomer

Diastereomer (*E/Z*-isomer) product ratios of olefinic proton were determined by Nuclear Overhauser Effect (NOE) experiments irradiating the H_A proton. The *Z*-isomer characteristically displays an enhancement of adjacent CH_2N methylene protons and the aryl protons whist the *E*-isomer characteristic reveals an enhancement of the methylene protons of the CH_2Nu and CH_2N protons.

General Procedure:

A mixture of *N*-allenyl diketopiperazine (**306**) (1.0 mmol), aryl halide (1.05 mmol), amine nuclephile (1.2 mmol), cesium carbonate (2.0 mmol), $Pd(OAc)_2$ (10 mol%) and triarylphosphine (20 mol%) in acetonitrile was stirred at 60 °C for 2-24 h. After the reaction was completed, the reaction mixture was filtered through celite and the filtrate was concentrated under vacuo. Then the residue was purified by flash column chromatography.

2-[(2Z)-3-(3,4-Dichloro-phenyl)-4-morpholin-4-yl-but-2-en-1-yl]-hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione (320)



***Z*-isomer**

Prepared by the general procedure from 2-buta-2,3-dienyl-hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione **(306)** (100.0 mg, 0.485 mmol), 1,2-dichloro-4-iodobenzene (132.4 mg, 0.485 mmol), morpholine (51.0 μL, 0.582 mmol), cesium carbonate (316.0 mg, 0.970 mmol), $Pd(OAc)_2$ (10.9 mg, 0.0485 mmol) and tri-2-furylphosphine (22.5 mg, 0.097 mmol) in acetonitrile (5 mL) at 60 °C over 2 h. After work up ^{1}H-NMR analysis of the crude residue showed it to comprise a 95:5 *Z*/*E*-isomer mixture (two triplet signals at δ 5.81 ppm (*Z*-isomer) and 5.60 ppm (*E*-isomer)). The crude residue was purified by flash column chromatography eluting with 2% methanol-dichloromethane to afford the same mixture of 95:5 *Z*/*E*-isomer mixture (180.5 mg, 85%) as a brown oil. Crystallization of this mixture with dichloromethane-petroleum ether mixture provided the pure *Z*-isomer as a colourless amorphous solid. Mp: 127-128 °C.

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.54 (d, *J*=1.9 Hz, 1H, Ar*H*-2') , 7.38 (d, *J*=8.3 Hz, 1H, Ar*H*-5'), 7.26 (dd, *J*=1.9, 8.3 Hz, 1H, Ar*H*-6'), 5.81 (t, *J*=6.9 Hz, 1H, C*H*-11), 4.33 (dd, *J*=2.2, 6.9 Hz, 2H, CH_2-10), 4.14 (d, J_{AB}=16.3 Hz, 1H, CH*H*-3), 4.10 (m, 1H, C*H*-8), 3.87 (d, J_{AB}=16.3 Hz, 1H, C*H*H-3), 3.64 (m, 5H, C*H*-5, CH_2-3", CH_2-5"), 3.57 (m, 1H, C*H*-5), 3.37 (s, 2H, CH_2-13), 2.42 (m, 5H, C*H*-7, CH_2-2", CH_2-6"), 2.08 (m, 2H, C*H*-6, C*H*-7), 1.93 (m, 1H, C*H*-6).

NOE experiments (δ, % enhancement): Irradiation at δ 5.81 ppm (C*H*-11), showed enhancement at 7.38 (Ar*H*-5', 6.96%), 7.26 (Ar*H*-6', 4.71%), 4.33 (CH_2-10, 3.97%) and 4.14 (CH*H*-3, 1.07%).

^{13}C NMR (75 MHz, $CDCl_3$, δ): 167.54 (CO), 163.29 (CO), 141.95 (C), 139.28 (C), 132.69 (C), 131.92 (C), 130.52 (CH), 128.85 (CH), 127.92 (CH), 126.28 (CH), 67.29 (CH_2), 59.49 (CH), 57.56 (CH_2), 53.74 (CH_2), 51.86 (CH_2), 45.72 (CH_2), 44.25 (CH_2), 29.33 (CH_2), 23.03 (CH_2).

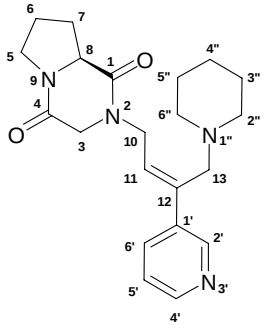
IR (ν_{max}, cm^{-1}): 3054 (CH-aromatic), 2961, 2892, 2858, 2821 (CH_2), 1667 (C=O), 1455, 1422, 1351, 1298, 1266 (C=C), 1228, 1028 (C-O).

ESI-MS (*m/z*, % rel. intensity): 438 (100, $[M]^+$), 440 (74), 442 (16).

Optical rotation: $[\alpha]_D^{22}$ = -54.8 (*c* 0.97, $CHCl_3$).

Anal. calcd for $C_{21}H_{25}{}^{35}Cl_2N_3O_3.0.5H_2O$: C, 56.38; H, 5.85; N, 9.39. Found: C, 56.65; H, 5.70; N, 9.20.

2-[(2Z)-4-Piperidin-1-yl-3-pyridin-3-yl-but-2-en-1-yl]-hexahydro-pyrrolo[1,2-a] pyrazine-1,4-dione (321)



***Z*-isomer**

Prepared by the general procedure from 2-buta-2,3-dienyl-hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione **(306)** (100.0 mg, 0.485 mmol), 3-iodopyridine (132.4 mg, 0.485 mmol), piperidine (58.0 μL, 0.582 mmol), cesium carbonate (316.0 mg, 0.970 mmol), $Pd(OAc)_2$ (10.9 mg, 0.0485 mmol) and tri-2-furylphosphine (22.5 mg, 0.097 mmol) in acetonitrile (5 mL) at 60 °C over 2 h. After work up ^{1}H-NMR analysis of the crude residue showed it comprised a 93:7 *Z*/*E*-isomer mixture (two triplet signals at δ 5.81 ppm (*Z*-isomer) and 5.70 ppm (*E*-isomer)). Purification by flash column chromatography eluting with 5% methanol-dichloromethane afforded a 94:6 *Z*/*E*-isomer mixture (119.0 mg, 67%) as a pale brown oil.

^{1}H and ^{13}C spectral data is for the ***Z*-isomer** in the mixture. **^{1}H-NMR** (500 MHz, $CDCl_3$, δ): 8.68 (d, *J*=1.9 Hz, 1H, Ar*H*-2'), 8.50 (d, *J*=4.8 Hz, 1H, Ar*H*-4'), 7.77 (d, *J*=7.9 Hz, 1H, Ar*H*-6'), 7.24 (dd, *J*=4.8, 7.9 Hz, 1H, Ar*H*-5'), 5.81 (t, *J*=7.0, 1H, C*H*-11), 4.41 (dd, *J*=7.0, 15.3 Hz, 1H, CH*H*-10), 4.36 (dd, *J*=7.0, 15.3 Hz, 1H, C*H*H-10), 4.16 (d, J_{AB}=16.5 Hz, 1H, CH*H*-3), 4.13 (t, *J*=7.9 Hz, 1H, C*H*-8), 3.93 (d, J_{AB}=16.5 Hz, 1H, C*H*H-3), 3.62 (m, 2H, CH_2-5), 3.40 (br s, 2H, CH_2-13), 2.42 (m, 5H, C*H*-4, CH_2-2", CH_2-6"), 2.07 (m, 2H, C*H*-6, C*H*-7), 1.94 (m, 1H, C*H*-6), 1.53 (br s, 4H, CH_2-3", CH_2-5"), 1.41 (br s, 2H, CH_2-4").

NOE experiments (δ, % enhancement): Irradiation at δ 5.81 ppm (C*H*-11), showed enhancement at 8.50 (Ar*H*-4', 4.99%) and 7.77 (Ar*H*-6', 4.01%); Irradiation at δ 4.36-4.41 ppm (CH_2-10), showed enhancement at 5.81 (C*H*-11, 6.56%); Irradiation at δ 3.40 ppm (CH_2-13), showed enhancement at 8.50 (Ar*H*-4', 2.92%), 7.77 (Ar*H*-6', 2.79%), 4.36-4.41 (CH_2-10, 3.68%) and 2.42 (CH_2-2"/CH_2-6", 5.67%).

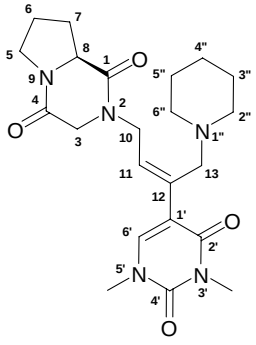
^{13}C-NMR (125 MHz, $CDCl_3$, δ): 167.62 (CO), 163.45 (CO), 148.89 (CH), 148.18 (C), 137.77 (C), 134.47 (CH), 128.13 (CH), 123.67 (CH), 59.10 (CH), 57.74 (CH_2), 54.72 (2×CH_2), 51.88 (CH_2), 45.67 (CH_2), 44.36 (CH_2), 29.30 (CH_2), 26.04 (2×CH_2), 24.05 (CH_2), 23.00 (CH_2).

IR (ν_{max}, cm^{-1}): 3049 (CH-aromatic), 2936, 2884, 2851 (CH_2), 1666 (C=O), 1455, 1341, 1297, 1264 (C=C), 1157, 1105 (C-O).

ES-MS (*m/z*, % rel. intensity): 369 (100, $[M+H]^+$).

HR-ES-MS (*m/z*): 369.2285 (calc. for $C_{21}H_{29}N_4O_2$, 369.2285 [M+H]).

2-[(2Z)-3-(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl)-4-piperidin -1- yl-but-2-en-1-yl]-hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione (322)



***Z*-isomer**

Prepared by the general procedure from 2-buta-2,3-dienyl-hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione **(306)** (100.0 mg, 0.485 mmol), 5-iodo-1,3-dimethyluracil (129.0 mg, 0.485 mmol), piperidine (58.0 μL, 0.582 mmol), cesium carbonate (316.0 mg, 0.970 mmol), $Pd(OAc)_2$ (10.9 mg, 0.0485 mmol) and tri-2-furylphosphine (22.5 mg, 0.097 mmol) in acetonitrile (5 mL) at 60 ^oC over 4 h. ^1H-NMR analysis of the crude residue showed it comprised a 29:71 *Z*/*E*-isomer mixture (two triplet signals at δ 5.95 ppm (*Z*-isomer) and 5.70 ppm (*E*-isomer)). Purification by flash column chromatography eluting with 5% methanol-dichloromethane gave a 32:68 *Z*/*E*-isomer mixture (194.3 mg, 93%) as a pale yellow oil which could not be separated by preparative HPLC analysis (30:70 v/v MeCN/H_2O, a LUNA 10μ C18(2), 250×4.6 mm modules reverse phase column, at λ 254 nm).

^{1}H-NMR (500 MHz, $CDCl_3$, δ): ***E*-isomer** (from the mixture); 7.33 (s, 1H, C*H*-6'), 5.70 (t, *J*=6.6 Hz, 1H, C*H*-11), 4.11 (d, J_{AB}=16.6 Hz, 1H, CH*H*-3), 4.07 (m, 1H, C*H*-8), 4.04 (dd, *J*=6.6 and 15.8 Hz, 1H, CH*H*-10), 3.96 (dd, *J*=6.6 and 15.8 Hz, 1H, C*H*H-10), 3.81 (d, J_{AB}=16.6 Hz, 1H, C*H*H-3), 3.57 (m, 2H, CH_2-5), 3.42 (s, 3H, NCH_3-3'), 3.35 (s, 3H, NCH_3-5'), 3.21 (s, 2H, CH_2-13), 2.35-2.49 (m, 5H, C*H*-7, CH_2-2", CH_2-6"), 2.08 (m, 2H, C*H*-6, C*H*-7), 1.94 (m, 1H, C*H*-6), 1.63 (m, 4H, CH_2-3", CH_2-5"), 1.45 (br s, 2H, CH_2-4").

NOE experiments (δ, % enhancement): Irradiation at δ 5.70 ppm (C*H*-11), showed enhancement at 4.04 (CH*H*-10, 1.56%), 3.96 (C*H*H-10, 1.27%), 3.21 (CH_2-13, 4.01%) and 2.49 (CH_2-2", CH_2-6", 1.73%); irradiation at δ 3.96 ppm (C*H*H-10), showed enhancement at 5.70 (C*H*-11, 3.60%) and 4.04 (CH*H*-10, 5.61%); irradiation at δ 3.21 ppm (CH_2-13), showed enhancement at 7.33 (C*H*-6', 1.44%), 5.70 (C*H*-11, 5.46%) and 2.49 (CH_2-2", CH_2-6", 6.40%).

^{1}H-NMR (500 MHz, $CDCl_3$, δ): ***Z*-isomer** (from the mixture); 7.52 (*s*, 1H, C*H*-6'), 5.95 (t, *J*=7.0 Hz, 1H, C*H*-11), 4.38 (dd, *J*=7.0 and 15.4 Hz, 1H, CH*H*-10), 4.20 (dd, *J*=7.0, 15.4 Hz, 1H, C*H*H-10), 4.17 (d, J_{AB}=16.6 Hz, 1H, CH*H*-3), 4.07 (m, 1H, C*H*-8), 3.87 (d, J_{AB}=16.6 Hz, 1H, C*H*H-3), 3.57 (m, 2H, CH_2-5), 3.41 (s, 3H, NCH_3-3'), 3.37 (s, 2H, CH_2-13), 3.35 (s, 3H, NCH_3-5'), 2.35-2.49 (m, 5H, C*H*-7, CH_2-2", CH_2-6"), 2.08 (m, 2H, C*H*-6, C*H*-7), 1.94 (m, 1H, C*H*-6), 1.63 (m, 4H, CH_2-3", CH_2-5"), 1.45 (br s, 2H, CH_2-4").

NOE experiment (δ, % enhancement): Irradiation at δ 5.95 ppm (C*H*-11), showed enhancement at 7.52 (C*H*-6', 3.67%), 4.38 (CH*H*-10, 1.56%), 4.20 (C*H*H-10, 2.20%) and 3.87 (C*H*H-3, 1.25%); irradiation at δ 4.38 ppm (CH*H*-10), showed % enhancement at 5.95 (C*H*-11, 5.30%), 3.37 (CH_2-13, 5.77%), 2.49 (CH_2-2", CH_2-6", 2.92%), 1.63 (CH_2-3", CH_2-5", 3.03%) and 1.45 (CH_2-4", 1.43%); irradiation at δ 3.37 ppm (CH_2-13), showed % enhancement at 7.52 (C*H*-6', 3.85%), 4.38 (CH*H*-10, 2.87%), 4.20 (C*H*H-10, 2.86%) and 2.49 (CH_2-2", CH_2-6", 9.95%).

^{13}C-NMR (125 MHz, $CDCl_3$, δ): ***E*-isomer**; 167.53 (CO), 163.61 (CO), 162.26 (CO), 151.90 (CO), 142.89 (CH), 129.26 (CH), 114.85 (C), 109.89 (C), 65.00 (CH_2), 59.49 (CH), 54.37 (2×CH_2), 51.89 (CH_2), 45.63 (CH_2), 45.10 (CH_2), 37.51 (CH_3), 29.25 (CH_2), 28.57 (CH_3), 25.50 (2×CH_2), 24.22 (CH_2), 23.00 (CH_2).

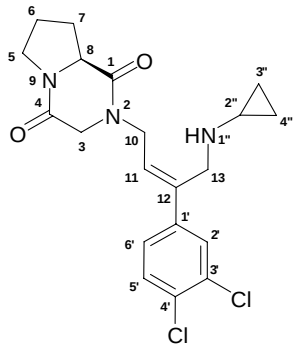
^{13}C-NMR (125 MHz, $CDCl_3$, δ): ***Z*-isomer**; 167.53 (CO), 163.51 (CO), 162.73 (CO), 151.80 (CO), 141.18 (CH), 128.80 (CH), 114.85 (C), 109.89 (C), 59.49 (CH), 57.16 (CH_2), 54.53 (2×CH_2), 51.80 (CH_2), 45.67 (CH_2), 43.87 (CH_2), 37.51 (CH_3), 29.32 (CH_2), 28.46 (CH_3), 25.97 (2×CH_2), 24.36 (CH_2), 23.02 (CH_2).

IR (ν_{max} cm^{-1}): 3054 (CH-alkene), 2936, 2890, 2851 (CH_2, CH_3), 1698, 1659 (C=O), 1455, 1341, 1297, 1270 (C=C).

ESI-MS (*m/z*, % rel. intensity): 430 (100, $[M+H]^+$).

HR-ES-MS (*m/z*): 430.2444 (calc. for $C_{22}H_{32}N_5O_4$, 430.2449 [M+H])**.**

2-[(2Z)-4-Cyclopropylamino-3-(3,4-dichloro-phenyl)-but-2-en-1-yl]hexahydro-pyrrolo[1,2-a]-pyrazine-1,4-dione (323)



***Z*-isomer**

Prepared by the general procedure from 2-buta-2,3-dienyl-hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione **(306)** (100.0 mg, 0.485 mmol), 1,2-dichloro-4-iodobenzene (132.4 mg, 0.485 mmol), cyclopropylamine (40.0 µL, 0.582 mmol),

cesium carbonate (316.0 mg, 0.970 mmol), $Pd(OAc)_2$ (10.9 mg, 0.0485 mmol) and tri-2-furylphosphine (22.5 mg, 0.097 mmol) in acetonitrile (5 mL) at 60 ^oC over 2 h. Work up and ^1H-NMR analysis of the crude residue showed it to comprise a 70:30 *Z*/*E*-isomer mixture (two triplet signals at δ 5.72 ppm (*Z*-isomer) and 5.59 ppm (*E*-isomer)). Purification by flash column chromatography eluting with 2% methanol-dichloromethane provided a 96:4 *Z*/*E*-isomer mixture (69.7 mg, 52%) as a pale yellow oil.

^1H and ^{13}C spectral data is for the ***Z*-isomer** (from the mixture). **^{1}H-NMR** (500 MHz, $CDCl_3$, δ): 7.51 (d, *J*=1.9 Hz, 1H, Ar*H*-2'), 7.39 (d, *J*=8.3 Hz, 1H, Ar*H*-5'), 7.25 (dd, *J*=1.9, 8.3 Hz, 1H, Ar*H*-6'), 5.72 (t, *J*=7.1 Hz, 1H, C*H*-11), 4.31 (d, *J*=7.1 Hz, 2H, CH_2-10), 4.15 (d, J_{AB}=16.6 Hz, 1H, CH*H*-3), 4.11 (t, *J*=7.9 Hz, 1H, C*H*-8), 3.88 (d, J_{AB}=16.6 Hz, 1H, C*H*H-3), 3.73 (s, 2H, CH_2-13), 3.60 (m, 2H, CH_2-5), 2.41 (m, 1H, C*H*-7), 2.08 (m, 4H, C*H*-6, C*H*-7, C*H*-2", N*H*-1"), 1.94 (m, 1H, C*H*-6), 0.44 (m, 2H, C*H*-3", C*H*-4"), 0.34 (m, 2H, C*H*-3", C*H*-4").

NOE experiments (δ, % enhancement): Irradiation at δ 5.72 ppm (C*H*-11), showed enhancement at 7.51 (Ar*H*-2', 7.02%), 7.25 (Ar*H*-6', 4.64%) and 4.31 (CH_2-10, 4.39%); irradiation at δ 4.31 ppm (CH_2-10), showed enhancement at 5.72 (C*H*-11, 5.35%), 3.88 (C*H*H-3, 2.33%) and 3.73 (CH_2-13, 3.34%); irradiation at δ 3.73 ppm (CH_2-13), showed enhancement at 7.51 (Ar*H*-2', 4.46%), 7.25 (Ar*H*-6', 3.61%), 4.31 (CH_2-10, 4.41%) and 2.08 (N*H*-1", 4.78%).

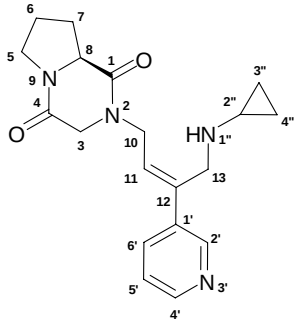
^{13}C-NMR (75 MHz, $CDCl_3$, δ): 167.11 (CO), 162.92 (CO), 141.24 (C), 141.02 (C), 132.64 (C), 131.68 (C), 130.39 (CH), 128.47 (CH), 125.77 (CH), 125.20 (CH), 59.08 (CH), 51.41 (CH_2), 47.36 (CH_2), 45.30 (CH_2), 43.73 (CH_2), 30.11 (CH), 28.92 (CH_2), 22.61 (CH_2), 6.51 (2×CH_2).

IR (ν_{max}, cm^{-1}): 3049 (CH-aromatic), 2978, 2950, 2884 (CH, CH_2), 1665 (C=O), 1596, 1456, 1297, 1262 (C=C).

ESI-MS (*m/z*, % rel. intensity): 408 (100, $[M]^+$), 410 (68), 412 (12).

HR-ES-MS (*m/z*): 408.1243 (calc. for $C_{20}H_{24}{}^{35}Cl_2N_3O_2$, 408.1240 [M+H])**.**

2-[(2Z)-4-Cyclopropylamino-3-pyridin-3-yl-but-2-en-1-yl)-hexahydropyrrolo-[1,2-a]pyrazine-1,4-dione (324)



***Z*-isomer**

Prepared by the general procedure from 2-buta-2,3-dienyl-hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione **(306)** (150.0 mg, 0.727 mmol), 3-iodopyridine (156.4 mg, 0.763 mmol), cyclopropylamine (60.0 µL, 0.582 mmol), cesium carbonate (472.8 mg, 1.454 mmol), $Pd(OAc)_2$ (16.3 mg, 0.0727 mmol) and tri-2-furylphosphine (33.8 mg, 0.1454 mmol) in acetonitrile (7.5 mL) at 60 ^oC over 3 h. Work up and ^1H-NMR analysis of the crude residue showed it comprised a 91:9 *Z*/*E*-isomer mixture (two triplet signals at δ 5.77 ppm (*Z*-isomer) and 5.70 ppm (*E*-isomer)). The crude residue was purified by flash column chromatography eluting with 4% methanol-dichloromethane to yield a 95:5 *Z*/*E*-isomer mixture (130.5 mg, 53%) as a yellow oil.

^1H and ^{13}C spectral data is for the ***Z*-isomer**. **^{1}H-NMR** (500 MHz, $CDCl_3$, δ): 8.66 (d, *J*=1.4 Hz, 1H, Ar*H*-2'), 8.51 (dd, *J*=1.4 and 4.7 Hz, 1H, Ar*H*-4'), 7.73 (d, *J*=7.9 Hz, 1H, Ar*H*-6'), 7.26 (dd, *J*=4.7 and 7.9 Hz, 1H, Ar*H*-5'), 5.77 (t, *J*=7.2 Hz, 1H, C*H*-11), 4.38 (dd, *J*=7.2 and 15.1 Hz, 2H, CH*H*-10), 4.31 (dd, *J*=7.2 and 15.1 Hz, 2H, C*H*H-10), 4.18 (d, J_{AB}=16.5 Hz, 1H, CH*H*-3), 4.12 (t, *J*=7.6 Hz, 1H, C*H*-8), 3.90 (d, J_{AB}=16.5 Hz, 1H, C*H*H-3), 3.81 (s, 1H, CH_2-13), 3.60 (m, 2H, CH_2-5), 2.42 (m,

2H, C*H*-7, N*H*-1"), 2.06-2.13 (m, 3H, C*H*-6, C*H*-7, C*H*-2"), 1.93 (m, 1H, C*H*-6), 0.45 (m, 2H, C*H*-3", C*H*-4"), 0.39 (m, 2H, C*H*-3", C*H*-4").

NOE experiments (δ, % enhancement): Irradiation at δ 5.77 ppm (C*H*-11), showed enhancement at 8.66 (Ar*H*-2', 5.91%), 7.73 (Ar*H*-6', 3.76%) and 4.38 (CH*H*-10, 3.69%); irradiation at δ 4.31 ppm (C*H*H-10), showed enhancement at 5.77 (C*H*-11, 2.58%), 3.90 (C*H*H-3, 2.16%) and 3.81 (CH_2-13, 1.86%); irradiation at δ 3.81 ppm (CH_2-13), showed enhancement at 8.66 (Ar*H*-2', 2.90%), 7.73 (Ar*H*-6', 3.17%), 4.31 (C*H*H-10, 3.80%), 2.08 (C*H*-2", 2.37%) and 0.39 (C*H*-3", C*H*-4", 1.03%).

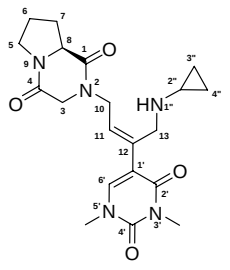
^{13}C-NMR (125 MHz, $CDCl_3$, δ): 167.19 (CO), 162.95 (CO), 148.89 (CH), 147.79 (CH), 140.14 (C), 136.49 (C), 133.87 (CH), 125.65 (CH), 123.28 (CH), 59.11 (CH), 51.47 (CH_2), 47.36 (CH_2), 45.30 (CH_2), 43.76 (CH_2), 30.17 (CH), 28.91 (CH_2), 22.62 (CH_2), 6.44 (2×CH_2).

IR ($\nu_{max,}$ cm^{-1}): 3049 (CH-aromatic), 2956, 2923, 2884 (CH_2), 1706, 1666 (C=O), 1457, 1415, 1358, 1297, 1262 (C=C).

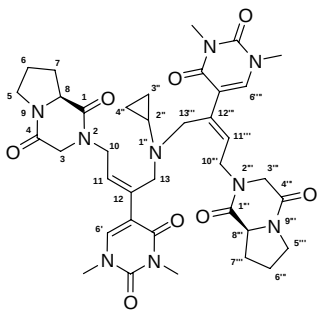
ESI-MS (*m/z*, % rel. intensity): 341 (100, $[M+H]^+$).

HR-ES-MS (*m/z*): 341.1967 (calc. for $C_{19}H_{29}N_4O_2$, 341.1972 [M+H])**.**

<u>2-[(2Z)-4-Cyclopropylamino-3-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl)-but-2-en-1-yl]-hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione (325)</u>



***Z*-isomer**



Dimer product, 357

Prepared by the general procedure from 2-buta-2,3-dienyl-hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione **(306)** (100.0 mg, 0.485 mmol), 5-iodo-1,3-dimethyluracil (129.0 mg, 0.485 mmol), cyclopropylamine (40.0 μL, 0.582 mmol), cesium carbonate (316.0 mg, 0.970 mmol), $Pd(OAc)_2$ (10.9 mg, 0.0485 mmol) and tri-2-furylphosphine (22.5 mg, 0.097 mmol) in acetonitrile (5 mL) at 60 ^oC over 2 h. Work up and ^{1}H-NMR analysis of the crude residue showed a complex mixture. The crude residue was purified by flash column chromatography eluting with 5% methanol-dichloromethane to give a mixture of 11:28:61 *Z*/*E* -isomer and a dimer product (94.5 mg, 49%) as a pale yellow oil.

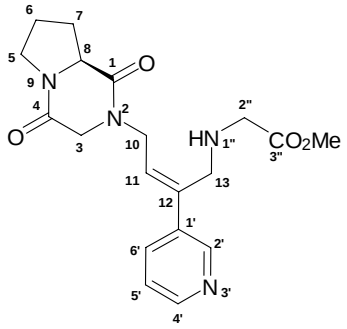
^{1}H-NMR assignments have been made for three products (where possible). **^{1}H-NMR** (500 MHz, C_6D_6 at 70 ^oC, δ): 7.10 (s, 1H, Ar*H*, dimer), 7.05 (s, 1H, Ar*H*-6',), 7.02 (s, 1H, Ar*H*', *Z*-isomer), 7.00 (s, 1H, Ar*H*, dimer), 5.95 (t, *J*=6.9 Hz, 1H, C*H*-11 or 11''', dimer), 5.84 (t, *J*=6.9 Hz, 1H, C*H*-11, *Z*-isomer), 5.69 (t, *J*=6.9 Hz, 1H, C*H*-11, *E*-isomer), 5.63 (t, *J*=6.8 Hz, 1H, C*H*-11 or 11''', dimer), 4.32 (dd, *J*=6.9 and 15.3 Hz, 1H, C*H*H-10, *Z*-isomer), 4.25 (dd, *J*=6.9, 15.3 Hz, 1H, C*H*H-10, dimer or 10'''), 4.14 (dd, *J*=6.9 and 15.3 Hz, 1H, CH*H*-10 or 10''', dimer), 4.08 (dd, *J*=6.9 and 15.3 Hz, 1H, C*H*H-10, *Z*-isomer), 3.66-3.99 (m, CH_2-10, *E*-isomer; CH_2-10 or 10''', dimer; CH_2-3, three products), 3.53-3.61 (m, C*H*-8), 3.38-3.47 (m, CH_2-13, C*H*H-5), 3.28-3.33 (m, N-CH_3-3'), 3.10 (m, CH*H*-5), 2.96-2.97 (m, N-CH_3-5'), 1.77-2.05 (m, CH_2-7, CH-2''), 1.25-1.50 (m, CH_2-6), 0.36-0.50 (m, CH_2-3'', CH_2-4'').

^{13}C-NMR (125 MHz, C_6D_6 at 70 ^oC, δ): 167.32, 167.31, 167.27, 162.99, 162.90, 162.79, 162.31, 162.10, 162.05, 151.58, 151.49, 151.28, 142.23, 142.13, 140.71, 136.15, 136.04, 136.00, 128.27, 128.09, 127.90, 126.64, 114.74, 110.82, 110.74, 61.74, 60.62, 59.05, 59.02, 53.60, 51.82, 51.76, 51.68, 45.15, 45.10, 44.72, 44.56, 43.75, 38.43, 38.10, 36.32, 36.31, 36.25, 36.22, 30.59, 29.95, 29.07, 29.05, 28.97, 27.96, 27.90, 2786, 22.60, 22.57, 7.54, 7.39, 7.28, 7.13.

IR (ν_{max}, cm^{-1}): 3417 (NH), 3055 (CH-alkene), 2983, 2956 (CH_2, CH_3), 1700, 1666 (C=O), 1456, 1421, 1341, 1266 (C=C).

ESI-MS (*m/z*, % rel. intensity): 402 (20, $[M+H]^+$), 746 (100, $[dimer+H]^+$), 768 (55, $[dimer+Na]^+$).

[4-(1,4-Dioxo-hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-2-pyridin-3-yl-but-2-enyl-amino]acetic acid methyl ester (326)



***Z*-isomer**

Prepared by the general procedure from 2-buta-2,3-dienyl-hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione **(306)** (206.3 mg, 1.0 mmol), 3-iodopyridine (215.3 mg, 1.05 mmol), glycine methyl ester hydrochloride (150.67 mg, 1.2 mmol), cesium carbonate (651.6 mg, 2.0 mmol), $Pd(OAc)_2$ (22.5 mg, 0.10 mmol) and tri-2-furylphosphine (46.44 mg, 0.20 mmol) in acetonitrile (10 mL) at 60 ^oC over 5 h. ^{1}H-NMR analysis of the crude residue showed it to comprise a 90:10 *Z*/*E*-isomer mixture (two triplet signals at δ 5.81 ppm (*Z*-isomer) and 5.72 ppm (*E*-isomer)). The crude residue was purified by flash column chromatography eluting with 3% methanol-dichloromethane to provide a 93:7 *Z*/*E*-isomer mixture (287.7 mg, 77%) as a pale yellow oil.

^{1}H and ^{13}C spectral data is for the ***Z*-isomer** (from the mixture). **^{1}H-NMR** (500 MHz, $CDCl_3$, δ): 8.69 (s, 1H, Ar*H*-2'), 8.52 (d, *J*=4.8 Hz, 1H, Ar*H*-4'), 7.80 (dt, *J*=1.7 and 7.9 Hz, 1H, Ar*H*-6'), 7.27 (dd, *J*=4.8 and 7.9 Hz, 1H, Ar*H*-5'), 5.81 (t, *J*=7.2 Hz, 1H, C*H*-11), 4.39 (dd, *J*=7.2 and 15.2 Hz, 1H, CH*H*-10), 4.33 (dd, *J*=7.2 and 15.2 Hz, 1H, *CH*H-10), 4.19 (d, J_{AB}=16.6 Hz, 1H, CH*H*-3), 4.12 (t, *J*=7.7 Hz, 1H, C*H*-8), 3.92 (d, J_{AB}=16.6 Hz, 1H, C*H*H-3), 3.74 (s, 3H, OCH_3), 3.73 (s, 2H, CH_2-2''),

3.64 (m, 1H, C*H*-5), 3.55 (m, 1H, C*H*-5), 3.42 (s, 2H, CH_2-13), 2.42 (m, 1H, C*H*-7), 2.07 (m, 3H, C*H*-6, C*H*-7, N*H*-1''), 1.91 (m, 1H, C*H*-6).

NOE experiment (δ, % enhancement): irradiation at δ 5.81 ppm (C*H*-11), showed enhancement at 8.69 (Ar*H*-2', 3.60%) and 7.80 (Ar*H*-6', 3.36%).

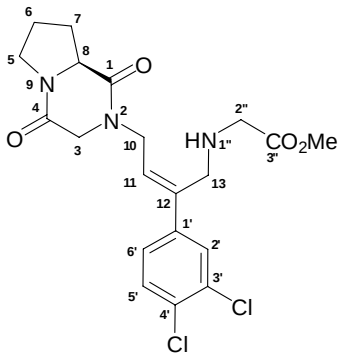
^{13}C-NMR (75 MHz, $CDCl_3$, δ): 173.28 (COO), 167.53 (CO), 163.38 (CO), 149.29 (CH), 148.03 (CH), 139.94 (C), 136.66 (C), 134.18 (CH), 126.65 (CH), 123.65 (CH), 59.47 (CH), 52.29 (OCH_3), 51.89 (CH_2), 50.23 (CH_2), 47.66 (CH_2), 45.69 (CH_2), 44.19 (CH_2), 29.29 (CH_2), 22.99 (CH_2).

IR (ν_{max}, cm^{-1}): 3346 (NH), 3054 (CH-aromatic), 2983, 2956, 2923, 2884 (CH_2, CH_3), 1739, 1670 (C=O), 1457, 1418, 1351, 1294, 1266 (C=C), 1220, 1023 (C-O).

ESI-MS (*m/z*, % rel. intensity): 373 (100, $[M+H]^+$).

HR-ES-MS (*m/z*): 373.1867 (calc. for $C_{19}H_{25}N_4O_4$, 373.1870 [M+H]).

[2-(3,4-Dichloro-phenyl)-4-(dioxo-hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-but-2-enylamino]-acetic acid methyl ester (327)



***Z*-isomer**

Prepared by the general procedure from 2-buta-2,3-dienyl-hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione **(306)** (206.3 mg, 1.0 mmol), 1,2-dichloro-4-iodobenzene (286.5 mg, 1.05 mmol), glycine methyl ester hydrochloride (150.67 mg, 1.2 mmol), cesium carbonate (651.6 mg, 2.0 mmol), $Pd(OAc)_2$ (22.5 mg, 0.10 mmol) and tri-2-furylphosphine (46.4 mg, 0.20 mmol) in acetonitrile (10 mL) at reflux over 2 h. ^{1}H-NMR analysis of the crude residue showed it to comprise a 95:5 *Z*/*E*-isomer mixture (two triplet signals at δ 5.78 ppm (*Z*-isomer) and 5.64 ppm (*E*-isomer)). The crude residue was purified by flash column chromatography eluting with 2% methanol-dichloromethane to give a 96:4 *Z*/*E*-isomer mixture (243.0 mg, 55%) as a pale yellow oil.

^{1}H and ^{13}C spectral data is for the ***Z*-isomer** (from the mixture). **^{1}H-NMR** (500 MHz, $CDCl_3$, δ): 7.57 (d, *J*=2.1 Hz, 1H, Ar*H*-2'), 7.39 (d, *J*=8.4 Hz, 1H, Ar*H*-5'), 7.30 (dd, *J*=2.1 and 8.4 Hz, 1H, Ar*H*-6'), 5.78 (t, *J*=7.2 Hz, 1H, C*H*-11), 4.32 (d, *J*=7.2 Hz, 2H, CH_2-10), 4.17 (d, J_{AB}=16.6 Hz, 1H, CH*H*-3), 4.11 (t, *J*=7.2 Hz, 1H, C*H*-8), 3.90 (d, J_{AB}=16.6 Hz, 1H, C*H*H-3), 3.75 (s, 3H, OCH_3), 3.67 (s, 2H, CH_2-2''), 3.63 (m, 1H, C*H*-5), 3.55 (m, 1H, C*H*-5), 3.42 (s, 2H, CH_2-13), 2.41 (m, 1H, C*H*-7), 2.06 (m, 2H, C*H*-6, C*H*-7), 1.92 (m, 1H, C*H*-6), 1.85 (br s, 1H, N*H*-1'').

NOE experiments (δ, % enhancement): irradiation at δ 5.78 ppm (C*H*-11), showed enhancement at 7.57 (Ar*H*-2', 6.43%), 7.30 (Ar*H*-6', 4.20%), 4.32 (CH_2-10, 3.56%) and 3.90 (C*H*H-3, 0.89%).

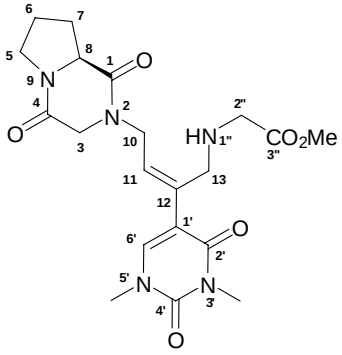
^{13}C-NMR (75 MHz, $CDCl_3$, δ): 173.28 (COO), 167.53 (CO), 163.38 (CO), 140.73 (C), 140.38 (C), 132.61 (C), 131.75 (C), 130.12 (CH), 128.36 (CH), 126.06 (CH), 125.71 (CH), 59.07 (CH), 51.91 (OCH_3), 51.52 (CH_2), 49.85 (CH_2), 47.32 (CH_2), 45.30 (CH_2), 43.83 (CH_2), 28.91 (CH_2), 22.60 (CH_2).

IR (ν_{max}, cm^{-1}): 3329 (NH), 3055 (CH-aromatic), 2986, 2950, 2890 (CH_2, CH_3), 1740, 1669 (C=O), 1456, 1423, 1297, 1265 (C=C), 1218, 1176, 1030 (C-O).

ESI-MS (*m/z*, % rel. intensity): 440 (100, $[M]^+$), 442 (78), 444 (14).

HR-ES-MS (*m/z*): 440.1139 (calc. for $C_{20}H_{23}Cl_2N_3O_4$, 440.1138 [M+H]).

[2-(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl)-4-(1,4-dioxo-hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-but-2-enylamino]-acetic acid methyl ester (328)



***Z*-isomer**

Prepared by the general procedure from 2-buta-2,3-dienyl-hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione **(306)** (100.0 mg, 0.485 mmol), 5-iodo-1,3-dimethyluracil (135.4 mg, 0.509 mmol), glycine methyl ester hydrochloride (73.1 mg, 0.582 mmol), cesium carbonate (316.0 mg, 0.970 mmol) and $Pd(PPh_3)_4$ (28.0 mg, 0.02425 mmol) in acetonitrile (5 mL) at refluxed over 18 h. ^{1}H-NMR analysis of the crude residue showed it to comprise a 27:73 *Z*/*E*-isomer mixture (two triplet signals at δ 5.85 ppm (*Z*-isomer) and 5.65 ppm (*E*-isomer)). The crude residue was purified by flash column chromatography eluting with 5% methanol-dichloromethane to afford a 32:68 *Z*/*E*-isomer mixture (110.3 mg, 52%) as a pale yellow oil.

^{1}H-NMR (500 MHz, $CDCl_3$, δ): ***E*-isomer** (from the mixture); 7.26 (s, 1H, C*H*-6'), 5.65 (t, *J*=6.8 Hz, 1H, C*H*-11), 4.04 (d, J_{AB}=16.7 Hz, 1H, CH*H*-3), 3.97 (m, 2H, CH*H*-10, C*H*-8), 3.90 (dd, *J*=6.8 and 15.4 Hz, 1H, C*H*H-10), 3.72 (d, J_{AB}=16.7 Hz, 1H, C*H*H-3), 3.65 (s, 3H, OCH_3), 3.45-3.57 (m, 2H, CH_2-5), 3.36 (s, 5H, CH_2-13,

NC*H*$_3$-3'), 3.31 (s, 2H, C*H*$_2$-2''), 3.27 (s, 3H, NC*H*$_3$-5'), 2.31 (m, 1H, C*H*-7), 2.02 (br s, 1H, N*H*-1''), 1.96 (m, 2H, C*H*-6, C*H*-7), 1.84 (m, 1H, C*H*-6).

NOE experiments (δ, % enhancement): irradiation at δ 5.65 ppm (C*H*-11), showed enhancement at 3.97 (C*H*H-10, 2.36%), 3.72 (C*H*H-3, 2.24%) and 3.36 (C*H*$_2$-13, 5.79%); irradiation at δ 3.36 ppm (C*H*H-10), showed enhancement at 7.26 (C*H*-6', 2.46%) and 5.65 (C*H*-11, 1.66%).

^{1}H-NMR (500 MHz, $CDCl_3$, δ): ***Z*-isomer** (from the mixture); 7.47 (s, 1H, C*H*-6'), 5.85 (t, *J*=6.8 Hz, 1H, C*H*-11), 4.27 (dd, *J*=6.8 and 15.4 Hz, 1H, CH*H*-10), 4.17 (dd, *J*=6.8 and 15.4 Hz, 1H, C*H*H-10), 4.11 (d, J_{AB}=16.7 Hz, 1H, CH*H*-3), 3.97 (m, 1H, C*H*-8), 3.87 (d, J_{AB}=16.7 Hz, 1H, C*H*H-3), 3.67 (s, 3H, OC*H*$_3$), 3.45-3.57 (m, 2H, C*H*$_2$-5), 3.48 (s, 2H, C*H*$_2$-13), 3.36 (s, 5H, C*H*$_2$-2'', NC*H*$_3$-3'), 3.27 (s, 3H, NC*H*$_3$-5'), 2.31 (m, 1H, C*H*-7), 2.02 (br s, 1H, N*H*-1''), 1.96 (m, 2H, C*H*-6, C*H*-7), 1.84 (m, 1H, C*H*-6).

NOE experiment (δ, % enhancement): irradiation at δ 5.85 ppm (C*H*-11), showed enhancement at 7.47 (C*H*-6', 4.62%) and 4.17-4.27 (C*H*$_2$-10, 4.40%); irradiation at δ 4.27 ppm (C*H*H-10), showed enhancement at 5.85 (C*H*-11, 4.71%), 4.17 (C*H*H-10, 15.75%), 3.48 (C*H*$_2$-13, 6.19%) and 3.36 (C*H*$_2$-2'', 7.94%); irradiation at δ 3.48 ppm (C*H*$_2$-13), showed enhancement at 7.47 (C*H*-6', 2.08%) and 4.27 (CH*H*-10, 2.50%).

^{13}C-NMR (125 MHz, $CDCl_3$, δ): ***Z*-isomer**; 171.73 (COO), 166.07 (CO), 162.08 (CO), 160.98 (CO), 150.50 (CO), 141.13 (CH), 134.72 (C), 125.03 (CH), 108.66 (C), 58.02 (CH), 53.72 (CH_2), 50.83 (CH_3), 50.52 (CH_2), 48.70 (CH_2), 44.22 (CH_2), 43.54 (CH_2), 36.08 (CH_3), 27.83 (CH_2), 27.11 (CH_3), 21.61 (CH_2).

^{13}C-NMR (125 MHz, $CDCl_3$, δ): ***E*-isomer**; 171.81 (COO), 166.17 (CO), 162.12 (CO), 161.42 (CO), 150.35 (CO), 139.89 (CH), 134.98 (C), 125.93 (CH),

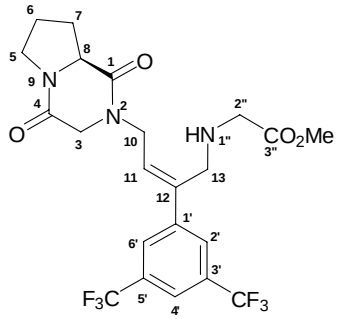
113.11 (C), 58.06 (CH), 50.82 (CH_3), 50.57 (CH_2), 49.16 (CH_2), 46.42 (CH_2), 44.22 (CH_2), 42.61 (CH_2), 36.06 (CH_3), 27.89 (CH_2), 27.04 (CH_3), 21.61 (CH_2).

IR ($\nu_{max,}$ cm^{-1}): 3335 (NH), 3055 (CH-alkene), 2983, 2956, 2884 (CH_2, CH3), 1736, 1700, 1667 (C=O), 1456, 1421, 1338, 1266 (C=C), 1207 (C-O).

ESI-MS (*m/z*, % rel. intensity): 434 (100, $[M+H]^+$).

HR-ES-MS (*m/z*): 434.2040 (calc. for $C_{20}H_{28}N_5O_6$, 434.2034 [M+H])**.**

[2-(3,5-Bis-trifluoromethyl-phenyl)-4-(dioxo-hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-but-2-enylamino]-acetic acid methyl ester (329)



***Z*-isomer**

Prepared by the general procedure from 2-buta-2,3-dienyl-hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione **(306)** (206.3 mg, 1.0 mmol), 1-iodo-3,5-bis(trifluoromethyl)benzene (158.0 μL, 1.05 mmol), glycine methyl ester hydrochloride (150.67 mg, 1.2 mmol), cesium carbonate (651.6 mg, 2.0 mmol), $Pd(OAc)_2$ (22.5 mg, 0.10 mmol) and tri-2-furylphosphine (46.4 mg, 0.20 mmol) in acetonitrile (10 mL) at 60 ^oC over 2 h. Work up and ^1H-NMR analysis of the crude residue showed it to comprise a 89:11 *Z*/*E*-isomer mixture (two triplet signals at δ 5.88 ppm (*Z*-isomer) and 5.65 ppm (*E*-isomer)). The crude residue was purified by flash column chromatography eluting with 3% methanol-dichloromethane to give a 90:10 *Z*/*E*-isomer mixture (268.1 mg, 53%) as a pale yellow oil. This mixture was

further separated by preparative HPLC analysis (40:60 v/v MeCN/H_2O, a LUNA 10µ C18(2), 250×4.6 mm modules reverse phase column, at λ 254 nm) to afford the pure *Z*-isomer as a pale yellow oil.

^{1}H and ^{13}C spectral data is for the ***Z*-isomer** (from the mixture). **^{1}H-NMR** (500 MHz, $CDCl_3$, δ): 7.95 (s, 2H, Ar*H*-2', Ar*H*-6'), 7.79 (s, 1H, Ar*H*-4'), 5.88 (t, *J*=7.1 Hz, 1H, C*H*-11), 4.38 (d, *J*=7.1 Hz, 2H, CH_2-10), 4.24 (d, J_{AB}=16.5 Hz, 1H, CH*H*-3), 4.12 (t, *J*=7.9 Hz, 1H, C*H*-8), 3.92 (d, J_{AB}=16.5 Hz, 1H, C*H*H-3), 3.75 (s, 3H, OCH_3), 3.73 (s, 2H, CH_2-2"), 3.64 (m, 2H, C*H*-5), 3.56 (m, 1H, C*H*-5), 3.44 (s, 2H, CH_2-13), 2.41 (m, 1H, C*H*-7), 2.12 (m, 2H, C*H*-6, C*H*-7), 1.92 (m, 2H, C*H*-6, N*H*-1").

NOE experiments (δ, % enhancement): irradiation at δ 5.88 ppm (C*H*-11), showed enhancement at 7.95 (Ar*H*-2', Ar*H*-6', 13.85%); irradiation at δ 4.38 ppm (CH_2-10), showed enhancement at 5.88 (C*H*-11, 5.13%), 3.92 (C*H*H-3, 2.30%) and 3.73 (CH_2-2", 4.20%).

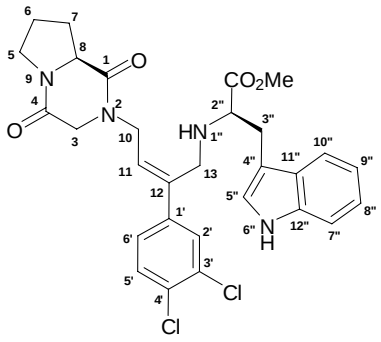
^{13}C-NMR (75 MHz, $CDCl_3$, δ): 173.30 (COO), 167.63 (CO), 163.24 (CO), 143.44 (C), 140.41 (C), 128.35 (CH), 126.98 (2×CH), 125.50 (C), 121.81 (CH), 59.46 (CH), 52.30 (OCH_3), 52.12 (CH_2), 50.24 (CH_2), 47.89 (CH_2), 45.71 (CH_2), 44.44 (CH_2), 29.28 (CH_2), 22.97 (CH_2).

IR (ν_{max}, cm^{-1}): 3322 (NH), 3049 (CH-aromatic), 2956, 2884 (CH_2, CH_3), 1740, 1667 (C=O), 1456, 1377, 1280 (C=C), 1179, 1132 (C-O).

ESI-MS (*m/z*, % rel. intensity): 508 (100, $[M+H]^+$).

Anal. calcd for $C_{22}H_{23}F_6N_3O_4.H_2O$: C, 51.16; H, 4.68; N, 8.13. Found: C, 51.46; H, 4.50; N, 8.20.

2-{3-(3,4-Dichloro-phenyl)-4-[1-(1H-indol-3-ylmethyl)-3-methoxy-2-oxopropyl-amino]-but-2-enyl}-hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione (330)



***Z*-isomer**

Prepared by the general procedure from 2-buta-2,3-dienyl-hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione **(306)** (206.3 mg, 1.0 mmol), 1,2-dichloro-4-iodobenzene (286.8 mg, 1.05 mmol), tryptophan methyl ester hydrochloride (305.7 mg, 1.2 mmol), cesium carbonate (651.6 mg, 2.0 mmol), $Pd(OAc)_2$ (22.5 mg, 0.10 mmol) and triphenylphosphine (52.5 mg, 0.20 mmol) in acetonitrile (10 mL) at reflux over 18 h. ^{1}H-NMR analysis of the crude residue showed it to comprise a 50:50 *Z*/*E*-isomer mixture (two triplet signals at δ 5.61 ppm (*Z*-isomer) and 5.43 ppm (*E*-isomer)). The crude residue was purified by flash column chromatography eluting with 3% methanol-dichloromethane to yield a >95% *Z*/*E*-isomer mixture (299.2 mg, 54%) as a pale yellow oil.

^{1}H and ^{13}C spectral data is for the ***Z*-isomer** (from the mixture). **^{1}H-NMR** (500 MHz, $CDCl_3$, δ): 7.52 (d, *J*=8.0 Hz, 1H, C*H*-10"), 7.41 (d, *J*=1.9, 1H, C*H*-2'), 7.31 (d, *J*=8.0, 1H, C*H*-7"), 7.16 (d, *J*=8.3 Hz, 1H, C*H*-5'), 7.15 (t, *J*=8.0 Hz, 1H, C*H*-9"), 7.07 (t, *J*=8.0 Hz, 1H, C*H*-8"), 7.03 (dd, *J*=1.9 and 8.3 Hz, 1H, C*H*-6'), 6.98 (d, *J*=1.8 Hz, 1H, C*H*-5"), 5.61 (t, *J*=7.1 Hz, 1H, C*H*-11), 3.97-4.08 (m, 3H, C*H*-8, CH_2-10), 3.91 (d, J_{AB}=16.6 Hz, 1H, CH*H*-3), 3.75 (s, 3H, OCH_3), 3.64 (d, J_{AB}=16.6 Hz, 1H, C*H*H-3), 3.61 (d, J_{AB}=12.5 Hz, 1H, 13-CH), 3.57 (dd, *J*=4.6 and 8.6 Hz, 1H, C*H*-2"), 3.49-3.68 (m, 2H, CH_2-5), 3.36 (d, J_{AB}=12.5 Hz, 1H, C*H*-13), 3.22 (dd, *J*=4.6,

14.4 Hz, 1H, CH*H*-3"), 2.98 (dd, *J*=8.6, 14.4 Hz, 1H, C*H*H-3"), 2.37 (m, 1H, C*H*-7), 2.02 (m, 2H, C*H*-6, C*H*-7), 1.89 (m, 2H, C*H*-6).

NOE experiments (δ, % enhancement): irradiation at δ 5.61 ppm (C*H*-11), showed enhancement at 7.41 (C*H*-2', 5.47%), 7.03 (C*H*-6', 2.89%) and 3.97-4.08 (CH_2-10, 1.42%); irradiation at δ 3.22 ppm (CH*H*-3"), showed enhancement at 3.57 (C*H*-2", 3.62%) and 2.98 (C*H*H-3", 16.02%); irradiation at δ 2.98 ppm (C*H*H-3"), showed enhancement at 7.52 (C*H*-10", 2.58%), 7.15 (C*H*-9", 1.18%), 6.98 (C*H*-5", 2.33%) and 3.22 (CH*H*-3", 14.05%).

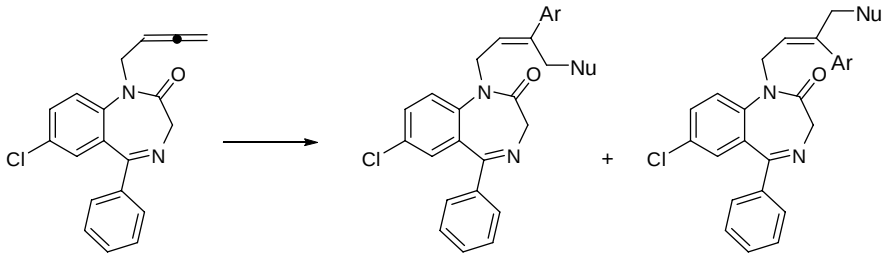
^{13}C-NMR (125 MHz, $CDCl_3$, δ): 174.85 (COO), 166.96 (CO), 163.12 (CO), 140.20 (C), 136.29 (C), 132.26 (C), 131.35 (C), 130.08 (CH), 128.07 (CH), 127.12 (C), 126.02 (CH), 125.45 (CH), 123.26 (CH), 122.01 (CH), 119.39 (CH), 118.47 (CH), 111.41 (CH), 110.80 (C), 60.95 (CH), 58.99 (CH_2), 52.02 (OCH_3), 51.02 (CH_2), 46.36 (CH_2), 45.28 (CH_2), 43.56 (CH_2), 29.06 (CH_2), 28.88 (CH_2), 22.54 (CH_2).

IR (ν_{max}, cm^{-1}): 3318 (NH), 3054 (CH-aromatic), 2983, 2953, 2884 (CH_2, CH_3), 1732, 1663 (C=O), 1457, 1341, 1294, 1265 (C=C), 1207, 1174, 1028 (CO).

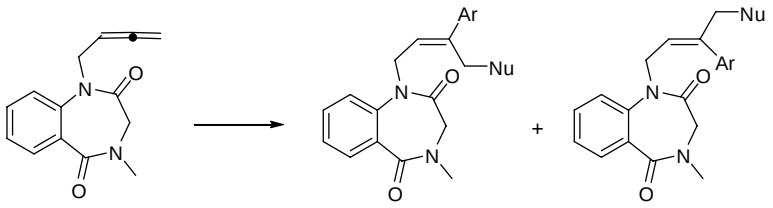
ESI-MS (*m/z*, % rel. intensity): 569 (100, $[M]^+$), 571 (72), 573 (16).

Anal. calcd for $C_{29}H_{30}{}^{35}Cl_2N_4O_4.0.5H_2O$: C, 60.02; H, 5.40; N, 9.68. Found: C, 59.85; H, 5.20; N, 9.35.

Palladium–Catalysed Cascade Reactions of 1,4-Benzodiazepine Derivatives



309 **316**, *Z*-isomer **317,** *E*-isomer



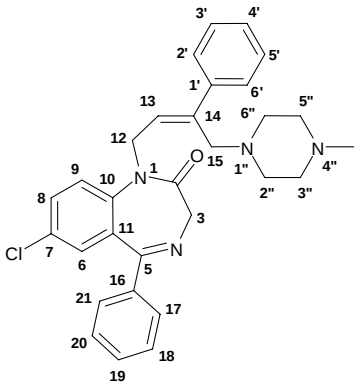
313 **318**, *Z*-isomer **319,** *E*-isomer

General Procedure:

A mixture of *N*-allenyl-1,4-benzodiazepine (**309** or **313**) (1.0 mol equiv), aryl iodide (1.05 mol equiv), *N*- or *C*-nucleophile (1.2 mol equiv), Cs_2CO_3 (2.0 mol equiv), $Pd(OAc)_2$ (10 mol %) and triarylphosphine (20 mol %) was dissolved in acetonitrile and stirred at 60 °C for 2–24 h. Then the reaction mixture was filtered through celite and the solids washed with 5% MeOH-CH_2Cl_2. The filtrate was evaporated under vacuo and the residue purified by flash column chromatography on silica gel.

Palladium–Catalysed Cascade Reactions with *N*-Nucleophile

7-Chloro-1-[4-(4-methyl-piperazin-1-yl)-3-phenylbut-2-enyl]-5-phenyl-1,3-dihydrobenzo[e][1,4]diazepin-2-one (331)



***Z*-isomer**

Prepared by the general procedure from 1-buta-2,3-dienyl-7-chloro-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one **(309)** (200 mg, 0.620 mmol), iodobenzene (73.0 μL, 0.650 mmol), *N*-methylpiperazine (82.0 μL, 0.743 mmol), Cs_2CO_3 (403.7 mg, 1.239 mmol), $Pd(OAc)_2$ (13.9 mg, 0.0620 mmol) and tri-2-furylphosphine (28.8 mg, 0.1239 mmol) in acetonitrile (10 mL) at 60 °C over 2 h. ^{1}H-NMR analysis of the crude residue showed it to comprise a 96:4 *Z*/*E*-isomer mixture (two triplet signals at δ 5.75 ppm (*Z*-isomer) and 5.48 ppm (*E*-isomer)). The crude residue was purified by flash column chromatography eluting with 5% methanol-dichloromethane to give a 97:3 *Z*/*E*-isomer mixture (267.7 mg, 87%) as a pale yellow solid. Mp: 61-62 ^{o}C.

^{1}H and ^{13}C spectral data is for the ***Z*-isomer** (from the mixture). **^{1}H-NMR** (500 MHz, $CDCl_3$, δ): 7.57 (dd, *J*=7.0, 1.6 Hz, 2H, ArH-2', ArH-6'), 7.36-7.49 (m, 5H, ArH), 7.20-7.29 (m, 6H, ArH), 5.75 (t, *J*=6.3 Hz, 1H, C*H*-13), 4.96 (dd, *J*=16.2 and 6.3 Hz, 1H, C*H*H-12), 4.86 (d, J_{AB}=10.6 Hz, 1H, C*H*H-3), 4.73 (dd, *J*=16.2 and 6.3 Hz, 1H, CH*H*-12), 3.81 (d, J_{AB}=10.6 Hz, 1H, CH*H*-3), 3.39 (d, *J*=13.2 Hz, 1H, C*H*H-15), 3.34 (d, *J*=13.2 Hz, 1H, CH*H*-15), 2.45 (br d, 8H, CH_2-2", CH_2-3", CH_2-5", CH_2-6"), 2.27 (s, 3H, NCH_3-4").

NOE experiment (δ, % enhancement): irradiation at δ 5.75 ppm (C*H*-13), showed enhancement at 7.57 (ArH-2'/ArH-6', 1.0 %), 7.43 (ArH, 1.9 %), 7.21 (ArH, 7.1 %), 4.96 (C*H*H-12, 1.6 %), 4.73 (CH*H*-12, 1.5 %).

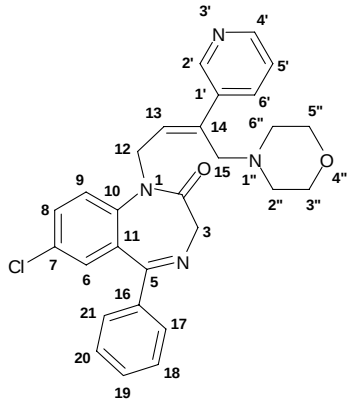
^{13}C-NMR (125 MHz, $CDCl_3$, δ): 169.50 (C), 169.45 (C), 142.34 (C), 141.89 (C), 139.78 (C), 138.67 (C), 131.77 (CH), 131.15 (C), 131.18 (CH), 130.23 (CH), 130.32 (C), 129.80 (2×CH), 128.89 (2×CH), 128.57 (2×CH), 128.39(CH), 127.76(CH), 126.83 (2×CH), 123.92 (CH), 58.02 (CH_2), 57.53 (CH_2), 55.50 (2×CH_2), 53.29 (2×CH_2), 46.33 (CH_3), 46.17 (CH_2).

IR (ν_{max}, cm^{-1}): 3056, 3027 (CH-aromatic), 2936, 2880, 2795 (CH_2), 1679 (C=O), 1609, 1481, 1446, 1405, 1356, 1322, 1294, 1282 (C=C).

ESI-MS (*m/z*, % rel. intensity): 499 (100, $[M+H]^+$).

Anal. calcd for $C_{30}H_{31}{}^{35}Cl_6N_4O.H_2O$: C, 69.62; H, 6.38; N, 10.83. Found: C, 71.10; H, 6.30; N, 10.55.

7-Chloro-1-(4-morpholin-4-yl-3-pyridin-3-ylbut-2-enyl)-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one (332)



***Z*-isomer**

Prepared by the general procedure from 1-buta-2,3-dienyl-7-chloro-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one (**309**) (200 mg, 0.620 mmol), 3-iodopyridine

(133.3 mg, 0.650 mmol), morpholine (65.0 μL, 0.743 mmol), Cs_2CO_3 (403.7 mg, 1.239 mmol), $Pd(OAc)_2$ (13.9 mg, 0.0620 mmol) and tri-2-furylphosphine (28.8 mg, 0.1239 mmol) in acetonitrile (10 mL) at 60 °C over 2 h. ^{1}H-NMR analysis of the crude residue showed it to comprise a 90:10 *Z*/*E*-isomer mixture (two triplet signals at δ 5.83 ppm (*Z*-isomer) and 5.60 ppm (*E*-isomer)). The crude residue was purified by flash column chromatography eluting with 5% methanol-dichloromethane to afford a 96:4 *Z*/*E*-isomer mixture (257.3 mg, 85%) as a pale yellow solid. Mp: 66-67 ^{o}C.

^{1}H and ^{13}C spectral data is for the ***Z*-isomer** (from the mixture). **^{1}H-NMR** (500 MHz, $CDCl_3$, δ): 8.56 (d, *J*=1.6 Hz, 1H, Ar*H*-2'), 8.47 (dd, *J*=1.6 and 4.8 Hz, 1H, Ar*H*-4'), 7.62 (td, *J*=1.6 and 8.0 Hz, 1H, Ar*H*-6'), 7.56 (d, *J*=7.2 Hz, 2H, Ar*H*), 7.47–7.51 (m, 2H, Ar*H*), 7.38–7.41 (m, 3H, Ar*H*), 7.30 (d, *J*=2.4 Hz, 1H, Ar*H*), 7.18 (dd, *J*=4.7 and 7.9 Hz, 1H, Ar*H*), 5.83 (t, *J*=6.4 Hz, 1H, C*H*-13), 5.01 (dd, *J*=6.4 and 16.2 Hz, 1H, C*H*H-12), 4.86 (d, J_{AB}=10.7 Hz, 1H, C*H*H-3), 4.67 (dd, *J*=6.4 and 16.2 Hz, 1H, CH*H*-12), 3.82 (d, J_{AB}=10.7 Hz, 1H, CH*H*-3), 3.59 (t, *J*=4.3 Hz, 4H, CH_2-3", CH_2-5"), 3.40 (d, *J*=13.3 Hz, 1H, C*H*H-15), 3.36 (d, *J*=13.3 Hz, 1H, CH*H*-15), 2.42 (m, 4H, CH_2-2", CH_2-6").

NOE experiment (δ, % enhancement): Irradiation at δ 5.83 ppm (C*H*-13), showed % enhancement at 8.56 (Ar*H*-2', 4.5 %), 7.62 (Ar*H*-6', 4.8 %), 7.30 (Ar*H*, 2.3 %), 5.01 (C*H*H-12, 1.6 %), 4.67 (CH*H*-12, 1.8 %).

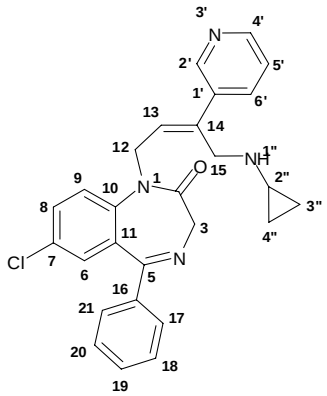
^{13}C-NMR (75 MHz, $CDCl_3$, δ): 169.45 (C), 169.35 (C), 148.92 (CH), 148.07 (CH), 141.54 (C), 138.45 (C), 137.25 (C), 136.79 (C), 134.31 (CH), 131.91 (CH), 131.56 (C), 131.29 (CH), 130.46 (C), 130.39 (CH), 129.76 (CH), 129.70 (2×CH), 128.95 (2×CH), 123.66 (CH), 123.40 (CH), 67.17 (2×CH_2), 57.65 (CH_2), 57.40 (CH_2), 53.70 (2×CH_2), 45.84 (CH_2).

IR (ν_{max}, cm^{-1}): 3050 (CH-aromatic), 2962, 2852, 2813 (CH_2), 1678 (C=O), 1608, 1481, 1446, 1406, 1356, 1323, 1265 (C=C), 1115, 1012 (C-O).

ESI-MS (*m/z*, % rel. intensity): 487 (100, $[M+H]^+$).

Anal. calcd for $C_{28}H_{27}{}^{35}ClN_4O_2.0.5H_2O$: C, 67.80; H, 5.69; N, 11.30. Found: C, 68.00; H, 5.65; N, 11.20.

7-Chloro-1-(4-cyclopropylamino-3-pyridin-3-ylbut-2-enyl)-5-phenyl-1,3-dihydro benzo[e][1,4]diazepin-2-one (333)



***Z*-isomer**

Prepared by the general procedure from 1-buta-2,3-dienyl-7-chloro-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one **(309)** (200 mg, 0.620 mmol), 3-iodopyridine (133.3 mg, 0.650 mmol), cyclopropylamine (51.0 μL, 0.743 mmol), Cs_2CO_3 (403.7 mg, 1.239 mmol), $Pd(OAc)_2$ (13.9 mg, 0.0620 mmol) and tri-2-furylphosphine (28.8 mg, 0.1239 mmol) in acetonitrile (10 mL) at 60 °C over 5 h. ^{1}H-NMR analysis of the crude residue showed it to comprise a 97:3 *Z*/*E*-isomer mixture (two triplet signals at δ 5.74 ppm (*Z*-isomer) and 5.70 ppm (*E*-isomer)). The crude residue was purified by flash column chromatography eluting with 3% methanol-dichloromethane to give the *Z*-isomer (162.7 mg, 57%) as a yellow solid. Mp: 70-71 ^{o}C.

^{1}H and ^{13}C spectral data is for the ***Z*-isomer**. **^{1}H-NMR** (500 MHz, $CDCl_3$, δ): 8.53 (d, *J*=1.7 Hz, 1H, Ar*H*-2'), 8.48 (d, *J*=3.9 Hz, 1H, Ar*H*-4'), 7.54–7.60 (m, 3H, Ar*H*), 7.45-7.50 (*m*, 2H, Ar*H*), 7.37–7.43 (m, 3H, Ar*H*), 7.29 (d, *J*=2.6 Hz, 1H, Ar*H*), 7.19 (dd, *J*=4.7 and 8.1 Hz, 1H, Ar*H*), 5.74 (t, *J*=6.5 Hz, 1H, C*H*-13), 4.97 (dd, *J*=6.5

and 15.8 Hz, 1H, C*H*H-12), 4.85 (d, J_{AB}=10.6 Hz, 1H, C*H*H-3), 4.65 (dd, *J*=6.5 and 15.8 Hz, 1H, CH*H*-12), 3.81 (d, J_{AB}=10.6 Hz, 1H, CH*H*-3), 3.73 (d, *J*=13.4 Hz, 1H, C*H*H-15), 2.99 (d, *J*=13.4 Hz, 1H, CH*H*-15), 2.06 (m, 1H, C*H*-2"), 0.39 (m, 2H, C*H*-3", C*H*-4"), 0.29 (m, 2H, C*H*-3", C*H*-4").

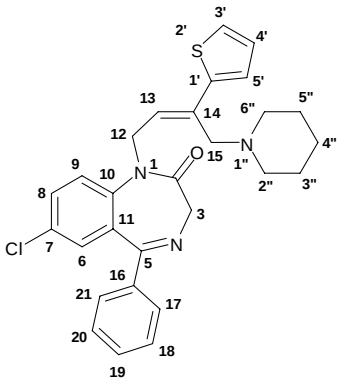
^{13}C-NMR (75 MHz, $CDCl_3$, *δ*): 168.95 (2×C), 148.73 (CH), 147.67 (CH), 141.17 (C), 138.97 (C), 138.08 (C), 136.40 (C), 133.78 (CH), 131.48 (CH), 131.19 (C), 130.82 (CH), 130.03 (C), 129.94 (CH), 129.31 (2×CH), 128.51 (2×CH), 127.07 (CH), 123.35 (CH), 123.20 (CH), 57.01 (CH_2), 47.52 (CH_2), 45.44 (CH_2), 30.14 (CH), 6.51 (2×CH_2).

IR (ν_{max}, cm^{-1}): 3396 (NH), 3005 (CH-aromatic), 2934, 2851 (CH_2), 1679 (C=O), 1609, 1481, 1446, 1408, 1361, 1323 (C=C).

ESI-MS (*m/z*, % rel. intensity): 457 (100, $[M+H]^+$).

HR-ESI (*m/z*): 457.1785 (calc. for $C_{27}H_{26}{}^{35}ClN_4O$, 457.1795 [M+H])**.**

7-Chloro-5-phenyl-1-(4-piperidin-1-yl-3-thiophen-2-ylbut-2-enyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one (334)



***E*-isomer**

Prepared by the general procedure from 1-buta-2,3-dienyl-7-chloro-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one **(309)** (200 mg, 0.620 mmol), 2-iodothiophene (72.0 μL, 0.650 mmol), piperidine (74.0 μL, 0.743 mmol), Cs_2CO_3 (403.7 mg, 1.239 mmol), $Pd(OAc)_2$ (13.9 mg, 0.0620 mmol) and tri-2-furylphosphine (28.8 mg, 0.1239 mmol) in acetonitrile (10 mL) at 60 °C over 6 h. ^{1}H-NMR analysis of the crude residue showed it to comprise an 93:7 *E*/*Z*-isomer mixture (two triplet signals at δ 5.45 ppm (*Z*-isomer) and 5.88 ppm (*E*-isomer)). The crude residue was purified by flash column chromatography eluting with 3% methanol-dichloromethane to give the *E*-isomer (226.1 mg, 74%) as a pale yellow oil.

^{1}H and ^{13}C spectral data is for the ***E*-isomer**. **^{1}H-NMR** (500 MHz, $CDCl_3$, δ): 7.56 (d, *J*=7.3 Hz, 2H, Ar*H*), 7.44 (m, 6H, Ar*H*), 7.12 (d, *J*=5.2 Hz, 1H, Ar*H*), 7.08 (d, *J*=3.4 Hz, 1H, Ar*H*), 6.91 (dd, *J*=3.8, 5.2 Hz, 1H, Ar*H*), 5.88 (t, *J*=6.4 Hz, 1H, C*H*-13), 4.99 (dd, *J*=6.4 and 16.4 Hz, 1H, C*H*H-12), 4.85 (d, J_{AB}=10.6 Hz, 1H, C*H*H-3), 4.72 (dd, *J*=6.4 and 16.4 Hz, 1H, CH*H*-12), 3.81 (d, J_{AB}=10.6 Hz, 1H, CH*H*-3), 3.29-3.36 (m, 2H, CH_2-15), 2.45 (br s, 4H, CH_2-2", CH_2-6"), 1.58 (br s, 4H, CH_2-3", CH_2-5"), 1.43 (br s, 2H, CH_2-4").

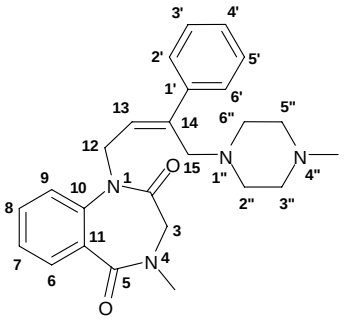
^{13}C-NMR (125 MHz, $CDCl_3$, δ): 169.13 (C), 169.06 (C), 145.20 (C), 141.21 (C), 138.27 (C), 131.40 (CH), 131.20 (C), 130.68 (CH), 129.77 (CH), 129.38 (2×CH), 128.46 (2×CH), 127.17 (CH), 124.92 (CH), 124.13 (CH), 123.69 (CH), 57.96 (CH_2), 57.06 (CH_2), 54.38 (2×CH_2), 45.53 (CH_2), 25.48 (2×CH_2), 23.93 (CH_2).

IR (ν_{max}, cm^{-1}): 3063 (CH-aromatic), 2933, 2853 (CH_2), 1680 (C=O), 1609, 1481, 1446, 1405, 1350, 1323, 1266 (C=C).

ESI-MS (*m/z*, % rel. intensity): 490 (100, $[M+H]^+$).

HR-ESI (*m/z*): 490.1699 (calc. for $C_{28}H_{29}{}^{35}ClN_3OS$ [M+H], 490.1720).

4-Methyl-1-[4-(4-methylpiperazin-1-yl)-3-phenylbut-2-enyl]-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (336)



***Z*-isomer**

Prepared by the general procedure from 1-buta-2,3-dienyl-4-methyl-3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione **(313)** (200 mg, 0.826 mmol), iodobenzene (111.0 μL, 0.867 mmol), *N*-methylpiperazine (97.0 μL, 0.991 mmol), Cs_2CO_3 (537.9 mg, 1.651 mmol), $Pd(OAc)_2$ (18.5 mg, 0.0826 mmol) and tri-2-furylphosphine (38.3 mg, 0.1651 mmol) in acetonitrile (10 mL) at 60 °C over 23 h. ^{1}H-NMR analysis of the crude residue showed it to comprise a 88:12 *Z*/*E*-isomer mixture (two triplet signals at δ 5.85 ppm (*Z*-isomer) and 5.57 ppm (*E*-isomer)). The crude residue was purified by flash column chromatography eluting with 5% methanol-dichloromethane to give a 98:2 *Z*/*E*-isomer mixture (177.9 mg, 52%) as a pale yellow solid. Mp: 49-50 ^{o}C.

^{1}H and ^{13}C spectral data is for the ***Z*-isomer**. **^{1}H-NMR** (500 MHz, $CDCl_3$, δ): 7.88 (dd, *J*=1.3, 7.7 Hz, 1H, Ar*H*), 7.48 (m, 1H, ArH, E isomer), 7.21-7.35 (m, 7H, Ar*H*), 5.85 (t, *J*=6.0 Hz, 1H, C*H*-13), 4.84 (dd, *J*=6.0, 16.3 Hz, 1H, C*H*H-12), 4.78 (dd, *J*=6.0 and 16.3 Hz, 1H, CH*H*-12), 4.11 (d, J_{AB}=14.5 Hz, 1H, C*H*H-3), 3.70 (d, J_{AB}=14.5 Hz, 1H, C*H*H-3), 3.41 (s, 2H, CH_2-15), 3.29 (s, 3H, NCH_3-4), 2.26-2.58 (m, 8H, CH_2-2", CH_2-3", CH_2-5", CH_2-6"), 2.29 (s, 3H, NCH_3-4").

NOE experiment (δ, % enhancement): Irradiation at δ 5.85 ppm (C*H*-13), showed % enhancement at 7.21 (Ar*H*-2'/Ar*H*-6', 8.5 %).

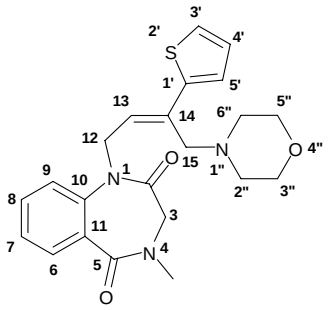
^{13}C-NMR (125 MHz, $CDCl_3$, δ): 168.01 (C), 167.24 (C), 141.91 (C), 140.22 (C), 138.94 (C), 131.97 (CH), 130.80 (CH), 129.27 (C), 128.39 (CH), 128.19 (2×CH), 127.34 (CH), 126.47 (2×CH), 125.93 (CH), 121.35 (CH), 57.66 (CH_2), 54.98 (2×CH_2), 53.25 (CH_2), 52.60 (2×CH_2), 46.66 (CH_3), 45.75 (CH_2), 36.03 (CH_3).

IR (ν_{max}, cm^{-1}): 3054 (CH-aromatic), 2937, 2879, 2799 (CH_2), 1677), 1647 (C=O), 1601, 1489, 1456, 1397, 1281, 1230 (C=C).

ESI-MS (*m/z*, % rel. intensity): 419 (100, $[M+H]^+$).

HR-ESI (*m/z*): 419.2435 (calc. for $C_{25}H_{31}N_4O_2$ [M+H], 419.2447).

4-Methyl-1-(4-morpholin-4-yl-3-thiophen-2-ylbut-2-enyl)-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (337)



***E*-isomer**

Prepared by the general procedure from 1-buta-2,3-dienyl-4-methyl-3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione **(313)** (200 mg, 0.826 mmol), 2-iodothiophene (96.0 µL, 0.867 mmol), morpholine (86.0 µL, 0.991 mmol), Cs_2CO_3 (537.9 mg, 1.651 mmol), $Pd(OAc)_2$ (18.5 mg, 0.0826 mmol) and triphenylphosphine (43.3 mg, 0.1651 mmol) in acetonitrile (10 mL) at 60 °C over 5 h. ^{1}H-NMR Analysis of the crude residue showed it to comprise an 53:47 *E*/*Z*-isomer mixture (two triplet signals at δ 5.51 ppm (*Z*-isomer) and 6.07 ppm (*E*-isomer)). The crude residue was

purified by flash column chromatography eluting with 25% acetone-hexane to afford a 55:45 *E*/*Z*-isomer mixture (238.6 mg, 70%) as a pale yellow oil.

^{1}H and ^{13}C spectral data is for both isomers. **^{1}H-NMR** (500 MHz, $CDCl_3$, δ): 7.88 (dd, *J*=1.7 and 8.1 Hz, 1H, Ar*H*, *E*-isomer), 7.83 (dd, *J*=1.7 and 8.1 Hz, 1H, Ar*H*, *Z*-isomer), 7.68 (d, *J*=12.0 Hz, 2H, Ar*H*, one isomer), 7.66 (dd, *J*=1.3 and 12.0 Hz, 2H, Ar*H*, one isomer), 6.85–7.56 (m, 4H, *E*-isomer, 4H, *Z*-isomer, Ar*H*), 6.07 (t, *J*=6.3 Hz, 1H, C*H*-13, *E*-isomer), 5.51 (t, *J*=6.3 Hz, 1H, C*H*-13, *Z*-isomer), 4.95 (dd, *J*=5.2 and 15.8 Hz, 1H, C*H*H-12, *Z*-isomer), 4.81 (dd, *J*=16.7 and 6.0 Hz, 1H, C*H*H-12, *E*-isomer), 4.72 (dd, *J*=16.7 and 6.0 Hz, 1H, CH*H*-12, *E*-isomer), 4.66 (dd, *J*=5.2, 15.8 Hz, 1H, C*H*H-12, *Z*-isomer), 4.12 (d, J_{AB}=14.5 Hz, 1H, C*H*H-3, *E*-isomer), 4.06 (d, J_{AB}=14.5 Hz, 1H, C*H*H-3, *Z*-isomer), 3.66–3.72 (m, 6H, CH*H*-3, *E*-isomer, CH*H*-3, *Z*-isomer, CH_2-3", CH_2-5", one isomer), 3.60–3.64 (m, 4H, CH_2-3", CH_2-5", one isomer, one isomer), 3.35 (br s, 2H, CH_2-15, *E*-isomer), 3.29 (s, 3H, NCH_3-4, *E*-isomer), 3.28 (s, 3H, NCH_3-4, *Z*-isomer), 3.10 (d, *J*=12.8 Hz, 1H, C*H*H-15, *Z*-isomer), 2.99 (d, *J*=12.8 Hz, 1H, CH*H*-15, *Z*-isomer), 2.47 (br s, 4H, CH_2-2", CH_2-6", *E*-isomer), 2.20–2.33 (m, 4H, CH_2-2", CH_2-6", *Z*-isomer).

NOE experiments (δ, % enhancement): irradiation at δ 6.07 ppm (C*H*-13, *E*-isomer), showed enhancement at 7.30 (Ar*H*, *E*-isomer, 3.6 %), 7.14 (Ar*H*, *E*-isomer, 5.5 %), 4.81 (C*H*H-12, *E*-isomer, 1.3 %), 4.72 (CH*H*-12, *E*-isomer, 1.3 %); irradiation at δ 5.51 ppm (C*H*-13, *Z*-isomer), showed enhancement at 6.87 (Ar*H*, *Z*-isomer, 1.8 %), 3.10 (C*H*H-15, *Z*-isomer, 2.5 %), 2.99 (CH*H*-15, *Z*-isomer, 2.7 %).

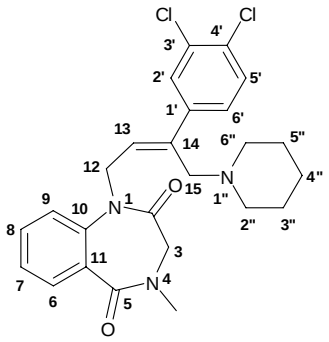
^{13}C-NMR (75 MHz, $CDCl_3$, δ): 168.38 (C), 168.36 (C), 167.57 (C), 167.43 (C), 145.21 (C), 140.56 (C), 139.93 (C), 139.68 (C), 133.58 (C), 132.57 (CH), 132.44 (CH), 132.38 (CH), 132.35 (CH), 132.20 (C), 132.13 (CH), 131.29 (CH), 131.17 (CH), 129.93 (C), 129.69 (C), 129.00 (CH), 128.84 (CH), 127.61 (CH), 127.52 (CH), 127.03 (CH), 126.7 (CH), 126.44 (CH), 126.11 (CH), 125.37 (CH), 124.49 (CH), 121.97 (CH), 121.65 (CH), 77.66 (CH), 67.38 (CH_2), 67.33 (CH_2), 66.44 (CH_2), 66.09 (CH_2) , 58.43 (CH_2) , 53.74 (CH_2), 53.61 (CH_2), 53.57 (CH_2), 53.35 (CH_2), 46.84 (CH_2), 45.66 (CH_2), 36.44(CH_2), 36.41 (CH_3).

IR (ν_{max}, cm^{-1}): 3071 (CH-aromatic), 2950, 2917, 2857 (CH_2), 1673), 1647 (C=O), 1596, 1476, 1451, 1397, 1267 (C=C), 1116 (C-O).

ESI-MS (*m/z*, % rel. intensity): 412 (100, $[M+H]^+$).

HR-ESI (*m/z*): 412.1678 (calc. for $C_{22}H_{26}N_3O_3{}^{32}S$ $[M+H]$, 412.1695).

1-[3-(3,4-Dichlorophenyl)-4-piperidin-1-ylbut-2-enyl]-4-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (338)



***Z*-isomer**

Prepared by the general procedure from 1-buta-2,3-dienyl-4-methyl-3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione **(313)** (200 mg, 0.826 mmol), 1,2-dichloro-4-iodobenzene (236.5 mg, 0.867 mmol), piperidine (98.0 μL, 0.991 mmol), Cs_2CO_3 (537.9 mg, 1.651 mmol), $Pd(OAc)_2$ (18.5 mg, 0.0826 mmol) and triphenylphosphine (43.3 mg, 0.1651 mmol) in acetonitrile (10 mL) at 60 °C over 7.5 h. ^{1}H-NMR analysis of the crude residue showed it to comprise a 81:19 *Z*/*E*-isomer mixture (two triplet signals at δ 5.85 ppm (*Z*-isomer) and 5.94 ppm (*E*-isomer)). The crude residue was purified by flash column chromatography eluting with 25% acetone-hexane to yield the product (273.4 mg, 70%) as a pale yellow oil which precipitated from diethyl ether-petroleum ether as an amorphous white powder comprising >97% *Z*-isomer. Mp: 134-135 ^oC.

^{1}H and ^{13}C spectral data is for the ***Z*-isomer**. **^{1}H-NMR** (500 MHz, $CDCl_3$, δ): 7.88 (d, *J*=7.7 Hz, 1H, Ar*H*-9), 7.50 (d, *J*=1.7 Hz, 1H, Ar*H*-2'), 7.47 (d, *J*=7.7 Hz, 1H, Ar*H*-8), 7.32 (d, *J*=8.6 Hz, 1H, Ar*H*-5'), 7.31 (dd, *J*=7.7, 8.6 Hz, 1H, Ar*H*-7), 7.28 (d, *J*=8.6 Hz, 1H, Ar*H*-6), 7.20 (dd, *J*=7.7 and 8.6 Hz, 1H, Ar*H*-6'), 5.85 (t, *J*=6.0 Hz, 1H, C*H*-13), 4.83 (dd, *J*=6.0 and 16.7 Hz, 1H, C*H*H-12), 4.75 (dd, *J*=6.0 and 16.7 Hz, 1H, CH*H*-12), 4.11 (d, J_{AB}=14.5 Hz, 1H, C*H*H-3), 3.70 (d, J_{AB}=14.5 Hz, 1H, CH*H*-3), 3.29 (s, 3H, NCH_3-4), 3.28 (s, 2H, CH_2-15), 2.35 (br s, 4H, CH_2-2", CH_2-6"), 1.51 (m, 4H, CH_2-3", CH_2-5"), 1.40 (m, 2H, CH_2-4").

NOE experiment (δ, % enhancement): irradiation at δ 5.85 ppm (C*H*-13), showed enhancement at 7.88 (Ar*H*-9, 5.8 %), 7.50 (Ar*H*-2', 2.4 %), 7.20 (Ar*H*-6', 4.4 %), 4.83 (C*H*H-12, 1.5 %), 4.75 (CH*H*-12, 1.5 %).

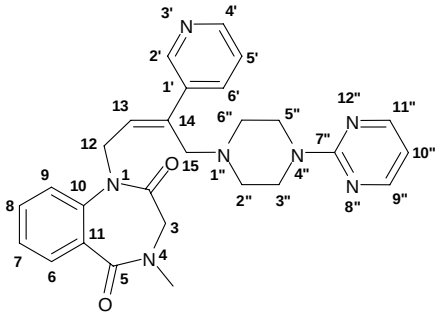
^{13}C-NMR (125 MHz, $CDCl_3$, δ): 168.04 (C), 167.18 (C), 142.50 (C), 140.53 (C), 137.66 (C), 132.49 (C), 132.37 (CH), 131.96 (C), 131.32 (CH), 130.34 (CH), 129.71 (CH), 128.94 (CH), 126.42 (CH), 121.6 (CH), 58.63 (CH_2), 54.85 (CH_2), 53.65 (CH_2), 46.90 (CH_2), 36.43 (CH_3), 26.39 (CH_2), 24.66 (CH_2).

IR (ν_{max}, cm^{-1}): 2934, 2857 (CH2), 1679, 1645 (C=O), 1602, 1473, 1399, 1262 (C=C).

ESI-MS (*m/z*, % rel. intensity): 472 (100, $[M]^+$), 474 (87), 476 (19).

Anal. calcd for $C_{25}H_{27}{}^{35}Cl_2N_3O_2$: C, 63.56; H, 5.76; N, 8.89; Cl, 15.01. Found: C, 63.30; H, 6.00; N, 8.65; Cl, 15.20.

4-Methyl-1-[3-pyridin-3-yl-4-(4-pyrimidin-2-ylpiperazin-1-yl)-but-2-enyl]-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (339)



***Z*-isomer**

Prepared by the general procedure from 1-buta-2,3-dienyl-4-methyl-3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione **(313)** (200 mg, 0.826 mmol), 2-(1-piperazinyl)pyrimidine dihydrochloride (230.6 mg, 0.867 mmol), morpholine (86.0 µL, 0.991 mmol), Cs_2CO_3 (537.9 mg, 1.651 mmol), $Pd(OAc)_2$ (18.5 mg, 0.0826 mmol) and triphenylphosphine (43.3 mg, 0.1651 mmol) in acetonitrile (10 mL) at 60 °C over 5 h. ^{1}H-NMR analysis of the crude residue showed it to comprise a 69:31 *Z*/*E*-isomer mixture (two triplet signals at δ 5.93 ppm (*Z*-isomer) and 5.67 ppm (*E*-isomer)). The crude residue was purified by flash column chromatography eluting with 4% methanol-dichloromethane to provide a 62:38 *Z*/*E*-isomer mixture (264.8 mg, 66%) as a pale yellow solid. Mp: 73-74 ^{o}C.

^{1}H-NMR (500 MHz, $CDCl_3$, δ): ***Z*-isomer**; 8.66 (s, 1H, Ar*H*-2'), 8.54 (m, 1H, Ar*H*-4'), 8.29 (m, 2H, Ar*H*-9", Ar*H*-11"), 7.88 (m, 1H, Ar*H*-6), 7.70 (d, *J*=8.1 Hz, 1H, Ar*H*-6'), 7.51 (m, 1H, Ar*H*), 7.27-7.33 (m, 2H, Ar*H*), 7.22 (dd, *J*=4.7 and 8.1 Hz, 1H, Ar*H*), 6.46 (m, 1H, Ar*H*-10"), 5.93 (t, *J*=6.0 Hz, 1H, C*H*-13), 4.82 (d, *J*=6.0 Hz, 2H, CH_2-12), 4.12 (d, J_{AB}=14.5 Hz, 1H, C*H*H-3), 3.74–3.78 (m, 4H, CH_2-3", CH_2-5"), 3.69 (d, J_{AB}=14.5 Hz, 1H, CH*H*-3), 3.43 (s, 2H, CH_2-15), 3.29 (s, 3H, NCH_3-4), 2.47–2.51 (m, 4H, CH_2-2", CH_2-6").

^{1}H-NMR (500 MHz, $CDCl_3$, δ): ***E*-isomer**; 8.56 (d, *J*=3.9 Hz, 1H, Ar*H*-2'), 8.54 (m, 1H, Ar*H*-4'), 8.29 (m, 2H, Ar*H*-9", Ar*H*-11"), 7.88 (m, 1H, Ar*H*-6), 7.51 (m, 1H, Ar*H*), 7.39 (t, *J*=6.8 Hz, 1H, Ar*H*), 7.27–7.33 (m, 2H, Ar*H*), 6.83 (d, *J*=8.6 Hz, 1H, Ar*H*), 6.46 (m, 1H, Ar*H*-10"), 5.67 (t, *J*=6.4 Hz, 1H, C*H*-13), 4.78 (dd, *J*=6.4, 15.8 Hz, 1H, C*H*H-12), 4.26 (dd, *J*=6.4 and 15.8 Hz, 1H, CH*H*-12), 4.03 (d, J_{AB}=14.5 Hz, 1H, C*H*H-3), 3.69–3.71 (m, 4H, CH_2-3", CH_2-5"), 3.65 (d, J_{AB}=14.5 Hz, 1H, CH*H*-3), 3.28 (s, 3H, NCH_3-4), 3.10 (s, 2H, CH_2-15), 2.17–2.32 (m, 4H, CH_2-2", CH_2-6").

NOE experiments (δ, % enhancement): irradiation at δ 5.93 ppm (C*H*-13, *Z*-isomer), showed enhancement at 8.66 (Ar*H*-2', *Z*-isomer, 4.0 %), 7.70 (Ar*H*-6', *Z*-isomer, 3.7 %), 7.28 (Ar*H*, *Z*-isomer, 3.0 %), 4.82 (C*H*H-12, *Z*-isomer, 3.0 %); irradiation at δ 5.67 ppm (C*H*-13, *E*-isomer), showed enhancement at 6.83 (Ar*H*, *E*-isomer, 1.5 %), 4.26 (CH*H*-12, *E*-isomer, 1.5 %), 7.28 (Ar*H*, *E*-isomer, 3.0 %), 3.10 (CH_2-15, *E*-isomer, 4.0 %).

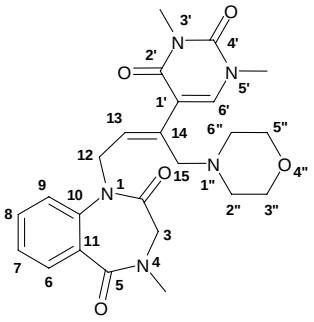
^{13}C-NMR (75 MHz, $CDCl_3$, δ): 168.40 (C), 168.20 (C), 167.52 (C), 167.35 (C), 162.02 (C), 161.96 (C), 158.11 (CH), 158.07 (CH), 149.57 (CH), 149.22 (CH), 148.96 (CH), 148.31 (CH), 140.32 (C), 139.49 (C), 138.41 (C), 137.40 (C), 136.71 (CH), 134.98 (C), 134.39 (CH), 132.45 (CH), 132.13 (CH), 131.38 (CH), 131.25 (CH), 130.07 (C), 129.82 (CH), 127.65 (CH), 126.57 (CH), 126.46 (CH), 123.54 (CH), 123.44 (CH), 122.05 (CH), 121.58 (CH), 110.26 (CH), 110.19 (CH), 65.84 (CH_2), 57.68 (CH_2), 53.58 (CH_2), 53.49 (CH_2), 53.21 (CH_2), 53.03 (CH_2), 46.68 (CH_2), 45.49 (CH_2), 44.04 (CH_2), 43.99 (CH_2), 36.44 (CH_2), 36.39 (CH_3).

IR (ν_{max}, cm^{-1}): 3031 (CH-aromatic), 2937, 2812 (CH_2), 1678, 1647 (C=O), 1586, 1547, 1481, 1448, 1397, 1358, 1257 (C=C).

ESI-MS (*m/z*, % rel. intensity): 484 (100, $[M+H]^+$).

Anal. calcd for $C_{27}H_{29}N_7O_2.H_2O$: C, 64.65; H, 6.03; N, 19.55. Found: C, 64.55; H, 5.90; N, 19.10.

1-[3-(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-4-morpholin-4-ylbut-2-enyl]-4-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (340)



***Z*-isomer**

Prepared by the general procedure from 1-buta-2,3-dienyl-4-methyl-3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione **(313)** (200 mg, 0.826 mmol), 5-iodo-1,3-dimethyluracil (230.6 mg, 0.867 mmol), morpholine (86.0 μL, 0.991 mmol), Cs_2CO_3 (537.9 mg, 1.651 mmol), $Pd(OAc)_2$ (18.5 mg, 0.0826 mmol) and triphenylphosphine (43.3 mg, 0.1651 mmol) in acetonitrile (10 mL) at 60 °C over 5 h. ^{1}H-NMR analysis of the crude residue showed it comprised a 85:15 *Z*/*E*-isomer mixture (two triplet signals at δ 5.86 ppm (*Z*-isomer) and 5.82 ppm (*E*-isomer)). The crude residue was purified by flash column chromatography eluting with 50% acetone-hexane to yield a 88:12 *Z*/*E*-isomer mixture (293.7 mg, 76%) as a colourless solid. Mp: 79-80 ^{o}C.

^{1}H and ^{13}C spectral data is for the ***Z*-isomer** (from the mixture). **^{1}H-NMR** (500 MHz, $CDCl_3$, δ): 7.80 (dd, *J*=1.3, 7.7 Hz, 1H, Ar*H*-6), 7.45 (ddd, *J*=1.3, 7.3 and 8.5 Hz, 1H, Ar*H*-8), 7.28 (dd, *J*=7.3 and 7.7 Hz, 1H, Ar*H*-7), 7.19 (d, *J*=8.5 Hz, 1H, Ar*H*-9), 7.17 (s, 1H, Ar*H*-6'), 5.86 (t, *J*=6.4 Hz, 1H, C*H*-13), 4.59 (dd, *J*=6.4 and 15.4 Hz, 1H, C*H*H-12), 4.30 (dd, *J*=6.4 and 15.4 Hz, 1H, CH*H*-12), 4.03 (d, *J*=14.6 Hz, 1H, C*H*H-3), 3.58–3.65 (m, 5H, CH*H*-3, CH_2-3", CH_2-5"), 3.37 (s, 3H, NCH_3), 3.31

(s, 3H, NC*H*$_3$), 3.22 (s, 3H, NC*H*$_3$), 3.05 (d, *J*=12.8 Hz, 1H, C*H*H-15), 2.94 (d, *J*=12.8 Hz, 1H, C*H*H-15), 2.29–2.37 (m, 4H, C*H*$_2$-2", C*H*$_2$-6").

NOE experiment (δ, % enhancement): irradiation at δ 5.86 ppm (C*H*-13), showed enhancement at 7.19 (Ar*H*-9, 3.5 %), 7.17 (Ar*H*-6', 5.7 %), 4.59 (C*H*H-12, 2.9 %).

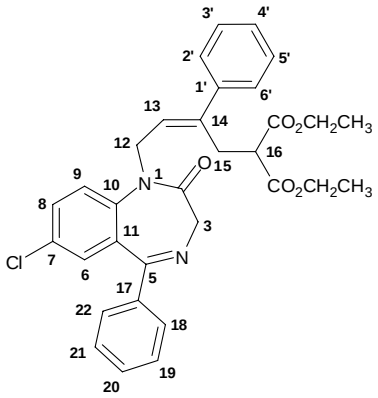
^{13}C-NMR (75 MHz, $CDCl_3$, δ): 167.99 (C), 167.47 (C), 161.89 (C), 151.71 (C), 142.41 (CH), 140.36 (C), 132.43 (C), 132.20 (CH), 130.85 (CH), 130.36 (CH), 129.89 (C), 126.29 (CH), 122.25 (CH), 110.76 (C), 67.36 (2×CH_2), 65.57 (CH_2), 53.58 (2×CH_2), 53.44 (CH_2), 46.98 (CH_2), 37.64(CH_3), 36.13(CH_3), 28.53 (CH_3).

IR (ν_{max}, cm^{-1}): 3054 (CH-aromatic), 2956, 2857, 2807 (CH_2, CH_3), 1700, 1676, 1647 (C=O), 1599, 1476, 1453, 1393, 1344, 1267 (C=C), 1115 , 1001 (C-O).

ESI-MS (*m/z*, % rel. intensity): 468 (100, $[M+H]^+$).

Anal. calcd for $C_{24}H_{29}N_5O_5.H_2O$: C, 59.37; H, 6.23; N, 14.42. Found: C, 59.60; H, 6.45; N, 14.15.

2-[4-(7-Chloro-2-oxo-5-phenyl-2,3-dihydrobenzo[e][1,4]diazepin-1-yl)-2-phenyl-but-2-enyl]-malonic acid diethyl ester (335)



***E*-isomer**

Prepared by the general procedure from 1-buta-2,3-dienyl-7-chloro-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one **(309)** (200 mg, 0.620 mmol), iodobenzene (73.0 μL, 0.650 mmol), diethylmalonate (113.0 μL, 0.743 mmol), Cs_2CO_3 (403.7 mg, 1.239 mmol), $Pd(OAc)_2$ (13.9 mg, 0.0620 mmol) and triphenylphosphine (32.5 mg, 0.1239 mmol) in 1,4-dioxane (10 mL) at 80 °C over 5 h. ^{1}H-NMR analysis of the crude residue showed it to comprise an 79:21 *E*/*Z*-isomer mixture (two triplet signals at δ 5.49 ppm (*Z*-isomer) and 5.62 ppm (*E*-isomer)). The crude residue was purified by flash column chromatography eluting with 40% acetone-hexane to provide an 81:19 *E*/*Z*-isomer mixture (189.5 mg, 55%) as a pale yellow oil which crystallised from EtOAc-petroleum ether as pale yellow needles to afford the *E*-isomer. Mp: 110-111 ^{o}C.

^{1}H and ^{13}C spectral data is for the ***E*-isomer**. **^{1}H-NMR** (500 MHz, $CDCl_3$, δ): 7.42–7.53 (m, 5H, Ar*H*), 7.37 (t, *J*=7.6 Hz, 2H, Ar*H*), 7.25-7.30 (m, 4H, Ar*H*), 7.19 (dd, *J*=1.8 and 7.9 Hz, 2H, Ar*H*-2', Ar*H*-6'), 5.62 (t, *J*=6.3 Hz, 1H, C*H*-13), 4.83 (d, J_{AB}=10.5 Hz, 1H, C*H*H-3), 4.82 (dd, *J*=6.3 and 16.2 Hz, 1H, C*H*H-12), 4.68 (dd, *J*=6.3 and 16.2 Hz, 1H, CH*H*-12), 4.12 (qd, *J*=5.2 and 7.1 Hz, 4H, CH-(CO-O-CH_2-

$CH_3)_2$), 3.79 (d, J_{AB}=10.5 Hz, 1H, CH*H*-3), 3.31 (t, *J*=7.6 Hz, 1H, C*H*-16), 3.13 (d, *J*=7.6 Hz, 2H, CH_2-15), 1.21 (td, *J*=2.2 and 7.1 Hz, 6H, CH-(CO-O-CH_2-CH_3)$_2$).

NOE experiments (δ, % enhancement): irradiation at δ 5.62 ppm (C*H*-13), showed enhancement at 7.19 (Ar*H*-2'/6', 10.66 %); irradiation at δ 4.68 ppm (CH*H*-12), showed enhancement at 7.43 (Ar*H*-9, 6.5 %), 5.62 (C*H*-13, 5.4 %), 4.82 (C*H*H-12, 7.4 %), 3.13 (CH_2-15, 3.6 %).

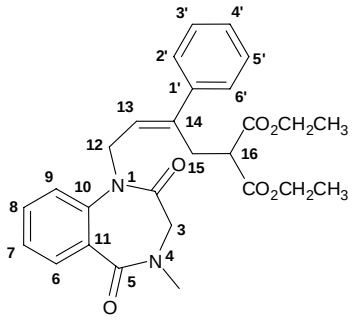
^{13}C-NMR (125 MHz, $CDCl_3$, δ): 169.49 (C), 169.30 (2×C), 141.55 (C), 140.14 (C), 139.18 (C), 138.29 (C), 131.46(CH), 131.05 (C), 130.15 (CH), 129.73 (CH), 129.37 (2×CH), 128.52 (2×CH), 128.43 (2×CH), 127.82 (CH), 127.16 (CH), 126.59 (2×CH), 123.61 (CH), 61.60 (2×CH_2), 57.08 (CH_2), 50.25 (CH), 46.23 (CH_2), 29.09 (CH_2), 14.02 (2×CH_3).

IR (ν_{max}, cm^{-1}): 3054 (CH-aromatic), 2956, 2926, 2851 (CH_2, CH_3), 1731, 1683 (C=O), 1610, 1482, 1446, 1406 1368, 1323, 1267 (C=C), 1229, 1155, 1031 (C-O).

ESI-MS (*m/z*, % rel. intensity): 559 (100, $[M]^+$), 561 (60).

Anal. calcd for $C_{32}H_{31}{}^{35}ClN_2O_5$: C, 68.75; H, 5.59; N, 5.01, Cl, 6.34. Found: C, 68.65; H, 5.75; N, 5.05, Cl, 6.40.

2-[4-(4-Methyl-2,5-dioxo-2,3,4,5-tetrahydro-benzo[e][1,4]diazepin-1-yl)-2-phenylbut-2-enyl]-malonic acid diethyl ester (341)



***E*-isomer**

Prepared by the general procedure from 1-buta-2,3-dienyl-4-methyl-3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione **(313)** (200 mg, 0.826 mmol), iodobenzene (111.0 µL, 0.650 mmol), diethylmalonate (150.0 µL, 0.991 mmol), Cs_2CO_3 (537.9 mg, 1.651 mmol), $Pd(OAc)_2$ (18.5 mg, 0.0826 mmol) and triphenylphosphine (43.3 mg, 0.1651 mmol) in 1,4-dioxane (10 mL) at 80 °C over 16 h. ^{1}H-NMR analysis of the crude residue showed it to comprise an 82:18 *E*/*Z*-isomer mixture (two triplet signals at δ 5.60 ppm (*Z*-isomer) and 5.66 ppm (*E*-isomer)). The crude residue was purified by flash column chromatography eluting with 20% acetone-hexane to give an 79:21 *E*/*Z*-isomer mixture (338.9 mg, 86%) as a pale yellow oil.

^{1}H and ^{13}C spectral data is for the ***E*-isomer**. **^{1}H-NMR** (500 MHz, $CDCl_3$, δ): 7.86 (dd, *J*=1.6 and 7.7 Hz, 1H, Ar*H*), 7.67 (m, 1H, Ar*H*), 7.44-7.54 (m, 2H, Ar*H*), 7.22-7.35 (m, 5H, Ar*H*), 5.66 (t, *J*=6.0 Hz, 1H, C*H*-13), 4.76 (dd, *J*=6.0 and 16.3 Hz, 1H, C*H*H-12), 4.72 (dd, *J*=6.0 and 16.3 Hz, 1H, CH*H*-12), 4.12 (m, 4H, CH-(CO-O-CH_2-CH_3)$_2$), 4.08 (d, J_{AB}=14.5 Hz, 1H, C*H*H-3), 3.68 (d, J_{AB}=14.5 Hz, 1H, CH*H*-3), 3.34 (t, *J*=7.6 Hz, 1H, C*H*-16), 3.27 (s, 3H, NCH_3-4), 3.17 (d, J=7.6 Hz, 2H, CH_2-15), 1.21 (t, J=7.1 Hz, 6H, CH-(CO-O-CH_2-CH_3)$_2$).

NOE experiments (δ, % enhancement): irradiation at δ 5.66 ppm (C*H*-13), showed enhancement at 7.23 (Ar*H*-2'/6', 12.76 %), 7.32 (Ar*H*-9, 3.2 %), 4.72 (CH*H*-

12, 3.3 %); irradiation at δ 4.72 ppm (CH*H*-12), showed enhancement at 7.32 (Ar*H*-9, 7.7 %), 5.66 (C*H*-13, 4.6 %), 3.17 (CH_2-15, 3.6 %).

^{13}C-NMR (125 MHz, $CDCl_3$, δ): 168.88 (C), 168.85 (C), 167.98 (C), 167.20 (C), 140.23 (C), 140.07 (C), 139.11 (C), 132.00 (CH), 130.79 (CH), 129.31 (C), 128.51 (2×CH), 127.79 (CH), 127.13 (CH), 126.67 (2×CH), 125.89, (CH), 121.37 (CH), 61.52 (CH_2), 61.53 (CH_2), 53.19 (CH_2), 50.22 (CH), 46.48 (CH_2), 35.97 (CH_3), 29.19 (CH_2), 14.01 (2×CH_3).

IR (ν_{max}, cm^{-1}): 3060 (CH-aromatic), 2981, 2928, 2868 (CH_2, CH_3), 1744, 1731, 1679, 1651 (C=O), 1599, 1478, 1445, 1397, 1369, 1270 (C=C), 1230, 1155, 1031 (C-O).

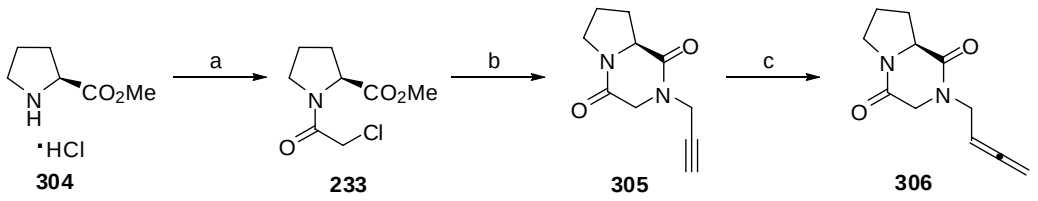
ESI-MS (*m/z*, % rel. intensity): 479 (100, $[M+H]^+$).

Anal. calcd for $C_{27}H_{30}N_2O_6$: C, 67.77; H, 6.32; N, 5.85. Found: C, 67.95; H, 6.75; N, 5.40.

RESULTS

1. Synthesis of *N*-allenyl diketopiperazine derivatives

N-Allenyl diketopiperazine, 2-buta-2,3-dienyl-hexahydro-pyrrolo[1,2-a] pyrazine-1,4-dione (**306**), was synthesized starting from *L*-proline methyl ester hydrochloride (**304**) as shown in **Scheme 66**.



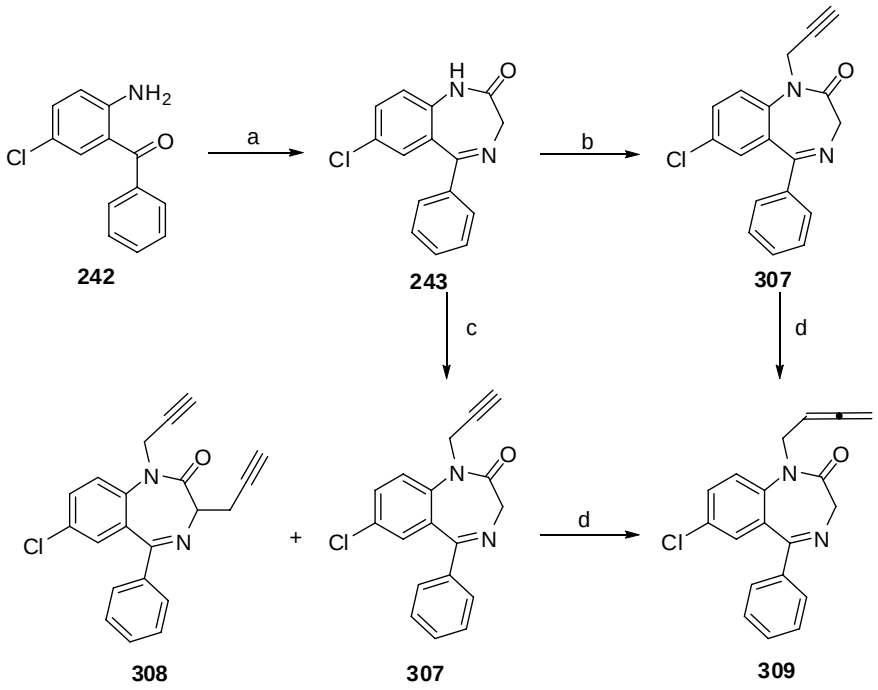
Scheme 66

Reagents and conditions:

a) Chloroacetyl chloride, Et_3N, CH_2Cl_2, 0 °C→rt, overnight.
b) Propargylamine, EtOH, 40 °C, overnight.
c) Paraformaldehyde, CuBr, Pr^i_2NH, 1,4-dioxane, reflux, 4h.

2. Synthesis of *N*-allenyl -5-phenyl-1,4-benzodiazepin-2-one derivatives

The synthesis of the *N*-allenyl -5-phenyl-1,4-benzodiazepin-2-one derivative 1-buta-2,3-dienyl-7-chloro-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one (**309**), was accomplished in three steps as shown in **Scheme 67**.



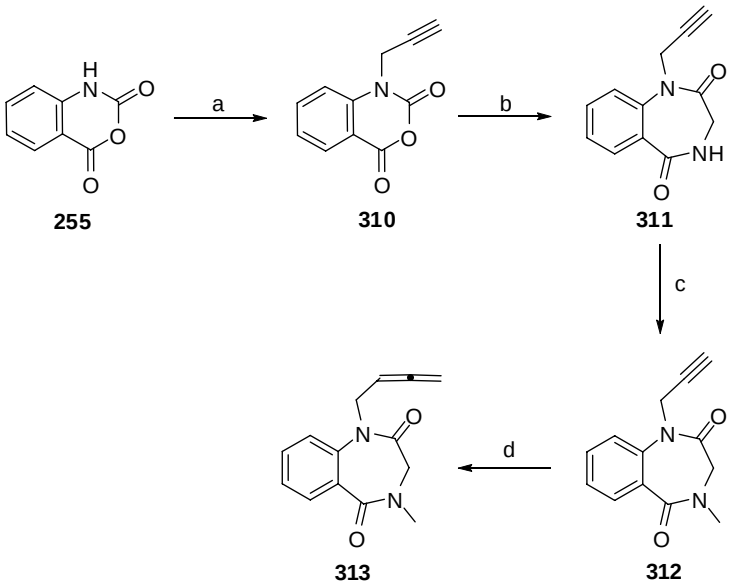
Scheme 67

Reagents and conditions:

a) Glycine ethyl ester hydrochloride, pyridine, reflux, 24h, 93%, 57% of starting material recovered.
b) Propargyl bromide (1.1 equiv.), NaH, DMF, 0 °C→rt, 3h, 88%.
c) Propargyl bromide (1.5 equiv.), NaH, DMF, 0 °C→rt, 14h, 60% (**307**), 20% (**308**).
d) Paraformaldehyde, CuBr, $Pr^{i}_{2}NH$, 1,4-dioxane, reflux, 14h, 75%.

3. Synthesis of *N*-allenyl-1,4-benzodiazepin-2,5-dione derivatives

1-Buta-2,3-dienyl-4-methyl-3,4-dihydro-1H-1,4-benzo-diazepine-2,5-dione (**313**) was prepared from isatoic anhydride (**255**) in four steps with an overall yield of 89% as shown in **Scheme 68**.



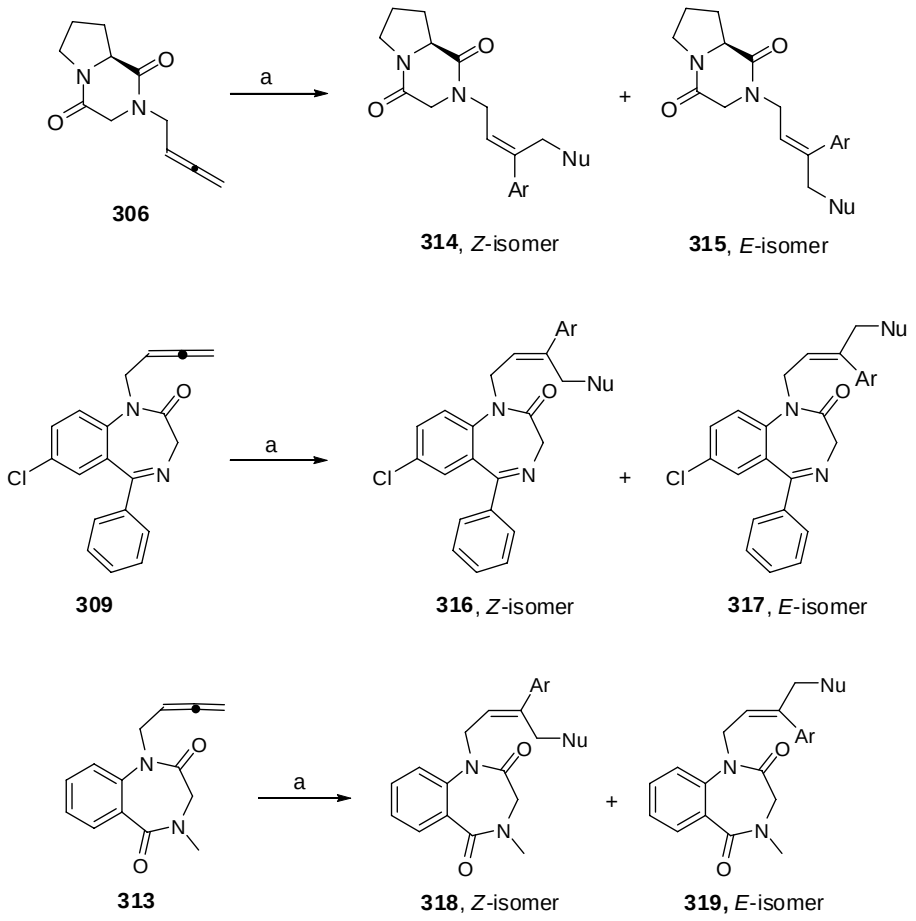
Scheme 68

Reagents and conditions:

a) Propargyl bromide (1.1 equiv.), NaH, DMF, 0 °C→rt, 6h, 84%.
b) Glycine, glacial acetic acid, reflux, 4h, 91%.
c) MeI, NaH, DMF, 0 °C→rt, 1h, 72%.
d) Paraformaldehyde, CuBr, $Pr^{i}_{2}NH$, 1,4-dioxane, reflux, 16h, 89%.

Three-Component Palladium-Catalysed Cascade Reaction

The Pd-catalysed cascade reaction between *N*-allenyl diketopiperazine (**315**) and *N*-allenyl-1,4-benzodiazepine (**318** and **323**) provided mixtures of *E*- and *Z*-isomers in good yield with the *Z*-isomer as the major product as shown in **Scheme 69** and **Tables 8, 9** and **10**.



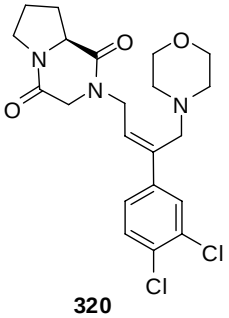
Scheme 69

Reagents and conditions:

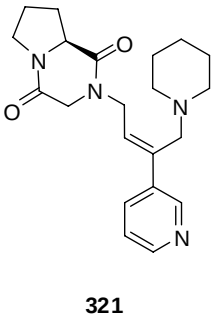
a) Aryl halide (1.05 mmol), amine (1.2 mmol), cesium carbonate (2.0 mmol), $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), acetonitrile, 2-24 h.

Some compounds were chosen to study and synthesize as shown below.

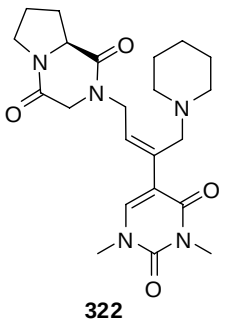
1) Diketopiperazine derivatives (320-330)



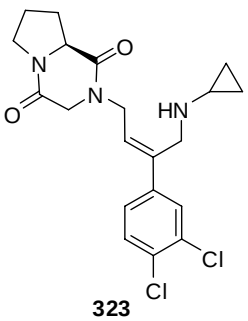
320



321



322



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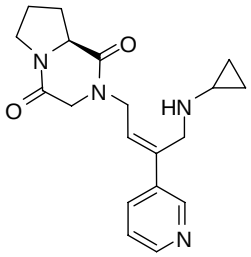

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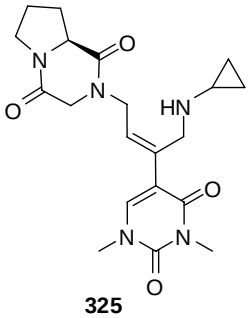

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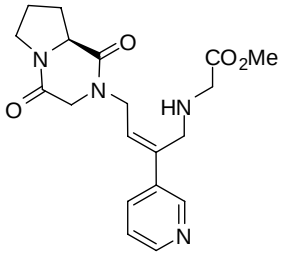

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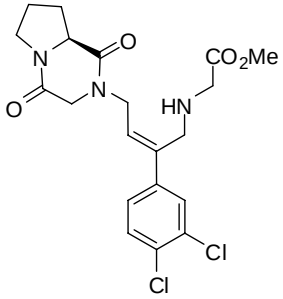

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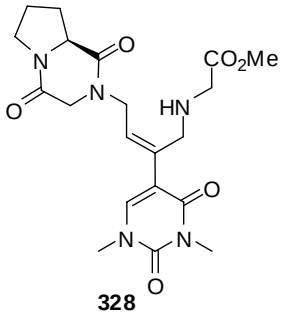

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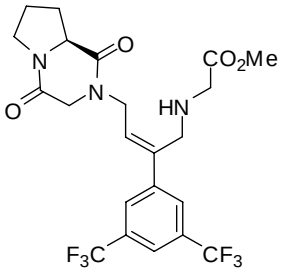

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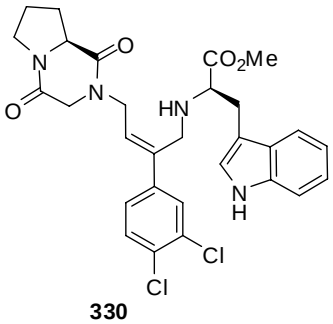
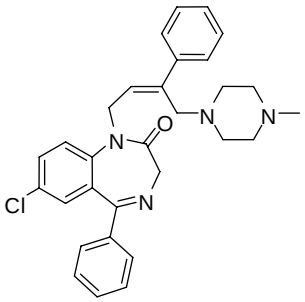


330

2) 5-Phenyl-1,4-benzodiazepin-2-one derivatives (331-335)



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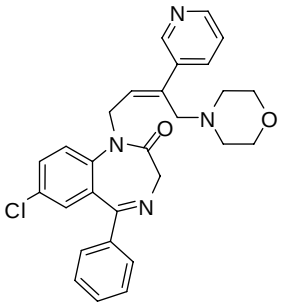
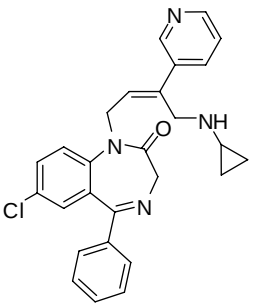


332



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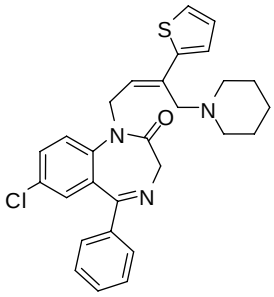

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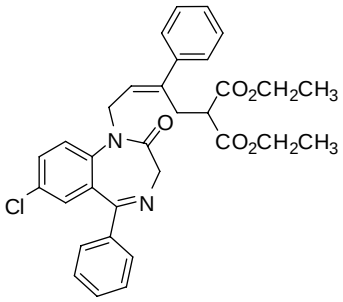
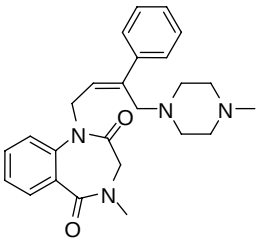
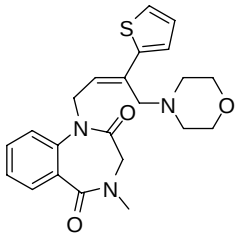


335

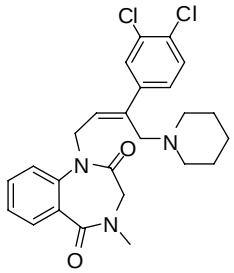
3) 1,4-Benzodiazepin-2,5-dione derivatives (336-341)



336



337



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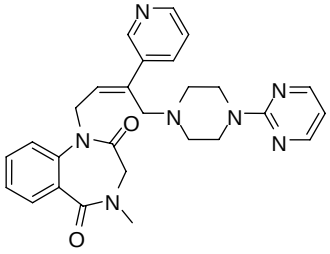
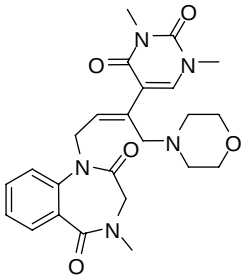
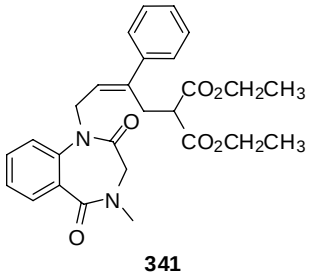


339

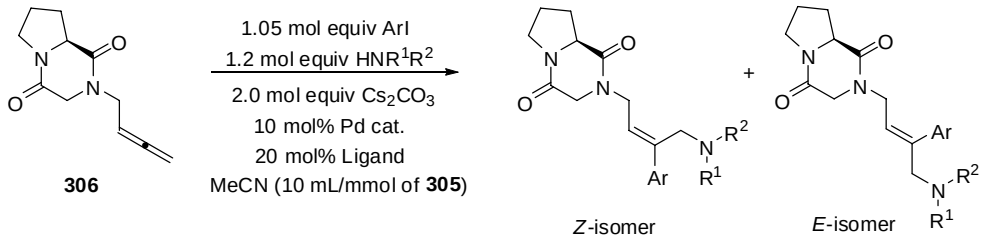


340



341

Table 8. Selective Palladium-catalysed cascade reaction of *N*-allenyl diketopiperazine derivative **306**.



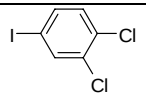
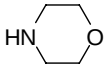
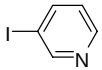
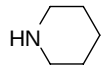
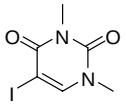
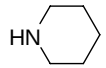
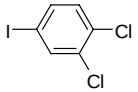
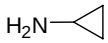
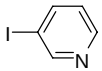
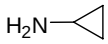
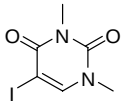
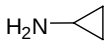
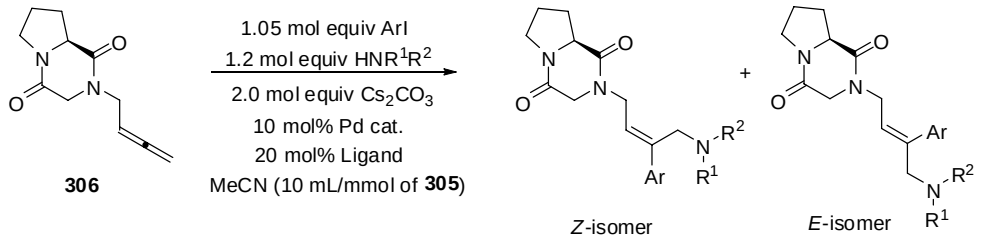
Entry	Aryl iodide	Nucleophile	Product	Catalyst	Solvent	Temperature (°C)	Reaction time (h)	% Conversion (*Z*, *E*-Isomer ratio)	% Yield (*Z*, *E*-Isomer ratio)
1			**320**	$Pd(OAc)_2$, TFP	MeCN	60	2	100 (95:5)	85 (95:5)
2			**321**	$Pd(OAc)_2$, TFP	MeCN	60	2	100 (93:7)	67 (94:6)
3			**322**	$Pd(OAc)_2$, TFP	MeCN	60	2	100 (30:70)	93 (32:68)
4			**323**	$Pd(OAc)_2$, TFP	MeCN	60	2	100 (70:30)	52 (96:4)
5			**324**	$Pd(OAc)_2$, TFP	MeCN	60	2	100 (65:35)	53 (95:5)
6			**325**	$Pd(OAc)_2$, TFP	MeCN	60	2	60 (>2 isomers)	49 (4 isomers)

Table 8. (Continued)



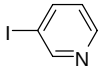
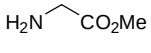
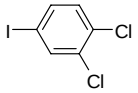
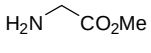
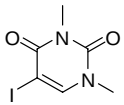
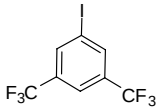
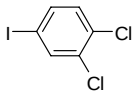
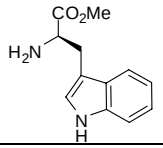
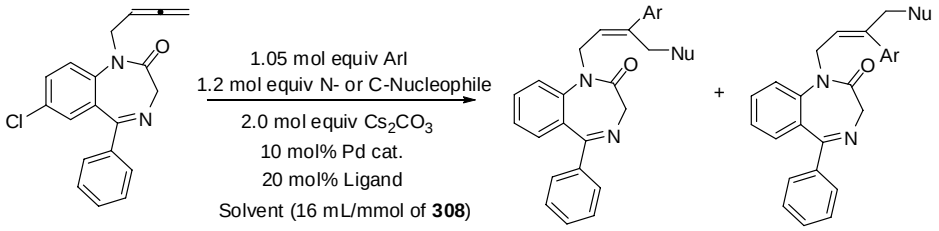
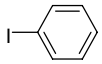
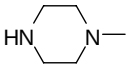
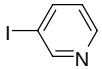
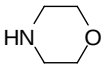
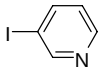
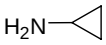
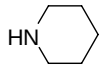
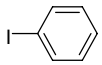
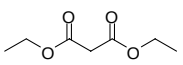
Entry	Aryl iodide	Nucleophile	Product	Catalyst	Solvent	Temperature (°C)	Reaction time (h)	% Conversion (*Z*, *E*-Isomer ratio)	% Yield (*Z*, *E*-Isomer ratio)
7			**326**	$Pd(OAc)_2$, TFP	MeCN	60	5	100 (90:10)	77 (93:7)
8			**327**	$Pd(OAc)_2$, TFP	MeCN	reflux	2	100 (95:5)	55 (96:4)
9			**328**	$Pd(PPh_3)_4$	MeCN	reflux	24	100 (27:73)	52 (32:68)
10			**329**	$Pd(OAc)_2$, TFP	MeCN	60	2	100 (89:11)	53 (90:10)
11			**330**	$Pd(OAc)_2$, TFP	MeCN	reflux	18	100 (50:50)	54 (>95%)

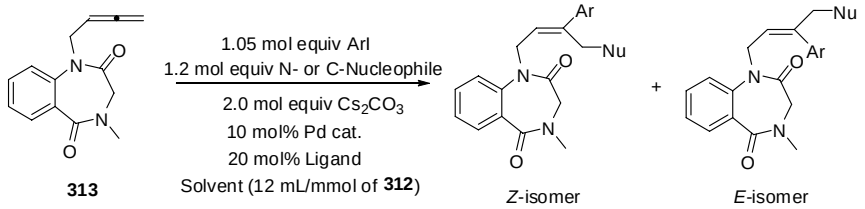
Table 9. Selective Palladium-catalysed cascade reaction of the *N*-allenyl -5-phenyl-1,4-benzodiazepin-2-one derivative **309**.

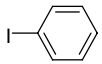
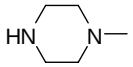
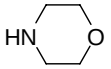
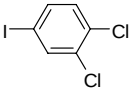
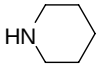
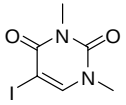
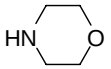
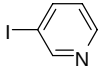
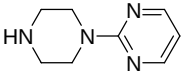
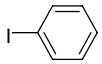
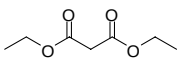


Entry	Aryl iodide	Nucleophile	Product	Catalyst	Solvent	Temperature (^{o}C)	Reaction time (h)	% Conversion (*Z*, *E*-Isomer ratio)	% Yield (*Z*, *E*-Isomer ratio)
1			**331**	$Pd(OAc)_2$, TFP	MeCN	60	2	100 (96:4)	87 (97:3)
2			**332**	$Pd(PPh_3)_4$	MeCN	60	2	100 (90:10)	85 (96:4)
3			**333**	$Pd(OAc)_2$, TFP	MeCN	60	5	100 (97:3)	57 (98:2)
4			**334**	$Pd(OAc)_2$, TFP	MeCN	60	6	100 (93:7)[a]	53 (99:1)[a]
5			**335**	$Pd(OAc)_2$, PPh_3	1,4-dioxane	80	5	100 (81:19)	55 (97:3)

[a]The S in thiophene ring reverses the *Z*/*E* assignement to *E*/*Z*-isomer ratio.

Table 10. Selective Palladium-catalysed cascade reaction of the *N*-allenyl-1,4-benzodiazepin-2,5-dione derivative **313**.

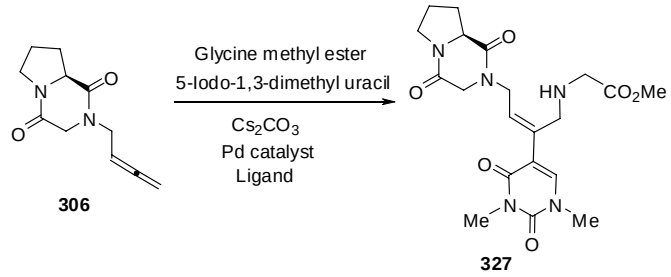


Entry	Aryl iodide	Nucleophile	Product	Catalyst	Solvent	Temperature (°C)	Reaction time (h)	% Conversion (*Z*, *E*-Isomer ratio)	% Yield (*Z*, *E*-Isomer ratio)
1			**336**	$Pd(OAc)_2$, TFP	MeCN	60	23	100 (88:12)	52 (98:2)
2			**337**	$Pd(OAc)_2$, TFP	MeCN	60	5	100 (53:47)[a]	70 (55:45)[a]
3			**338**	$Pd(OAc)_2$, TFP	MeCN	60	7.5	100 (81:19)	70 (97:3)
4			**339**	$Pd(OAc)_2$, TFP	MeCN	60	5	100 (85:15)	76 (88:12)
5			**340**	$Pd(OAc)_2$, TFP	MeCN	60	5	100 (69:31)	66 (62:38)
6			**341**	$Pd(OAc)_2$, PPh_3	1,4-dioxane	80	16	100 (82:18)[b]	86 (79:21)[b]

[a]the S in thiophene ring reverses the *Z*/*E* assignement to *E*/*Z*-isomer ratio.

[b]Diethyl malonate reverses the *Z*/*E* assignement to *E*/*Z*-isomer ratio.

Table 11. Attempted optimisation of the cascade reaction of *N*-allenyl diketopiperazine **306** with 5-iodo-1,3-dimethyl uracil and glycine methyl ester.

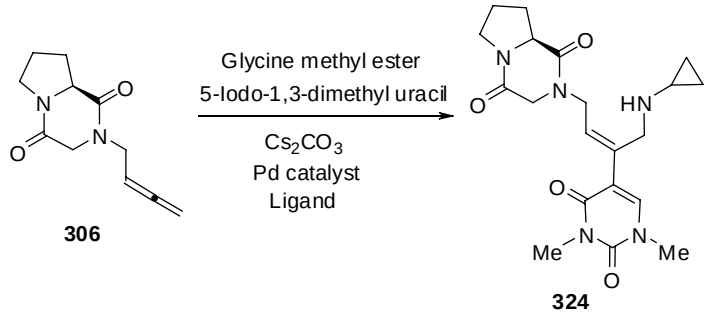


306 **327**

Entry	Catalyst[a]	Solvent	Temperature (°C)	Reaction Time (h)	% Conversion (*Z*/*E*-Isomer ratio)
1	$Pd(OAc)_2$, TFP	MeCN	60	2	100 (>2 isomers)
2	$Pd(OAc)_2$, TFP	MeCN	reflux	2	100 (>2 isomers)
3	$Pd(OAc)_2$, TFP	THF	60	2	100 (>2 isomers)
4	$Pd(OAc)_2$, TFP	DMF	60	2	Not complete
5	$Pd(OAc)_2$, TFP	MeCN[b]	60	2	100 (>2 isomers)
6	$Pd(OAc)_2$, TFP	MeCN[c]	60	2	100 (>2 isomers)
7	Pd_2dba_3	MeCN	60	2 days	30 (50:50)
8	Pd_2dba_3, TFP	MeCN	60	3 days	No reaction
9	Pd_2dba_3, TFP	MeCN	reflux	2 days	79 (37:46:17)
10[d]	$Pd(OAc)_2$, TFP	MeCN	60	2	100 (>2 isomers)
11	$Pd(OAc)_2$, Ph_3P	MeCN	60	5	100 (>2 isomers)
12	$Pd(OAc)_2$, TFP	MeCN	40	2 days	100 (>2 isomers)
13	$Pd(PPh_3)_4$	MeCN	60	4 days	38 (39:61)
14	$Pd(PPh_3)_4$	MeCN	reflux	18	83 (27:73)
15[e]	$Pd(PPh_3)_4$	MeCN	reflux	8	100 (41:59)
16[f]	$Pd(PPh_3)_4$	MeCN	reflux	8	86 (41:59)
17	$Pd(PPh_3)_4$	MeCN	reflux	1 day	100 (27:73)

[a]1.0 mol equiv *N*-allenyl diketopiperazine (**306**), 1.05 mol equiv 5-iodo-1,3-dimethyl uracil, 1.2 mol equiv glycine methyl ester, 2.0 mol equiv Cs_2CO_3, 10 mol% $Pd(OAc)_2$, 20 mol% ligand, solvent (10 mL/mmol of **306**); [b]20 mL of MeCN/mmol of **306** was used in the reaction; [c]5 mL of MeCN/mmol of **306** was used in the reaction; [d]2.0 mol equiv *N*-allenyl diketopiperazine (**306**), 2.05 mol equiv 5-iodo-1,3-dimethyl uracil and 1.2 mol equiv glycine methyl ester; [e]2.5 mol% CuI was added in the reaction; [f]1.0 mol equiv Et_4NCl was added in the reaction.

Table 12. Attempted optimisation of the cascade reaction of *N*-allenyl diketopiperazine **306** with 5-iodo-1,3-dimethyl uracil and cyclopropylamine.



Entry	Catalyst[a]	Solvent	Temperature (°C)	Reaction Time (h)	% Conversion (*Z*/*E*-Isomer ratio)
1	$Pd(OAc)_2$, TFP	MeCN	60	2	60 (>2 isomers)
2	$Pd(OAc)_2$, TFP	MeCN	reflux	2	61 (>2 isomers)
3	Pd_2dba_3, TFP	MeCN	60	3 days	10 (>2 isomers)
4	Pd_2dba_3, TFP	MeCN	reflux	2 days	53 (>2 isomers)
5	$Pd(OAc)_2$, TFP	MeCN[b]	60	18	Not complete
6	$Pd(OAc)_2$, TFP	DMF	80	2	100 (>2 isomers)

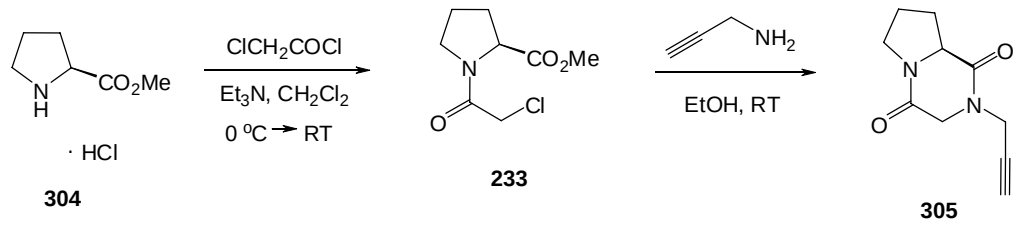
[a]1.0 mol equiv *N*-allenyl diketopiperazine (**306**), 1.05 mol equiv 5-iodo-1,3-dimethyl uracil, 1.2 mol equiv glycine methyl ester, 2.0 mol equiv Cs_2CO_3, 10 mol% $Pd(OAc)_2$, 20 mol% ligand, solvent (10 mL/mmol of **306**); [b]20 mL of MeCN/mmol of **306** was used in the reaction.

DISCUSSION

The objective of this work is application of the privileged substructure concept by synthesis of their derivatives using a palladium-catalysed three-component cascade reaction. *N*-Allenyl of three privileged heterocycles, prepared for the three-component reaction are *N*-allenyl diketopiperazine (**306**), *N*-allenyl-5-phenyl-1,4-benzodiazepin-2-one (**309**) and *N*-allenyl-1,4-benzodiazepin-2,5-dione derivatives (**313**).

Synthesis of *N*-allenyl diketopiperazine derivative (305)

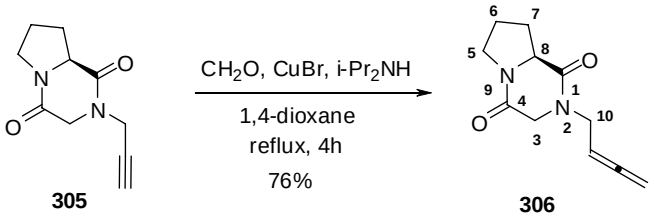
N-Allenyl diketopiperazine (**306**) was synthesized by homologation of *N*-propargyl diketopiperazine (**305**) which, in turn, was prepared from *L*-proline methyl ester hydrochloride (**304**) (**Scheme 70**) via *N*-acylation using chloroacetyl chloride and triethylamine in dichloromethane to provide **233** (Pandey *et al*., 2000), then diketopiperazine ring formation with propargylamine in ethanol to afford the desired product (**305**). (Baures *et al*., 1997)



Scheme 70

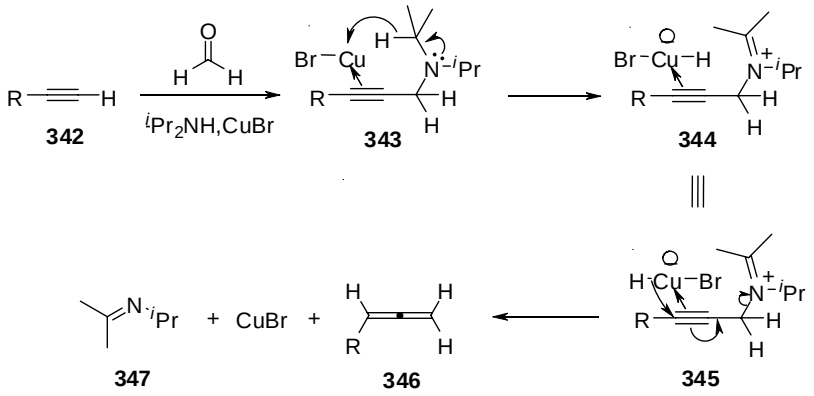
The Crabbé reaction is a simple one-pot reaction for the homologation of a terminal alkyne to afford the corresponding allene product in moderate to good yield. (Searles *et al*., 2000) A mixture of *N*-propargyl diketopiperazine (**305**), paraformaldehyde, diisopropylamine and catalytic amount of copper (I) bromide in 1,4-dioxane was stirred under reflux for 4h to yield 76% of allene product (**306**) (**Scheme 71**). The ^{1}H NMR (400 MHz) spectrum of this compound in $CDCl_3$ showed

a one proton quintet signal at δ 5.10 ppm which is a characteristic of the methine proton of the allene moiety and the methylene proton signal of the allene part showed a two proton multiplet at δ 4.85 ppm. The C-3 methylene protons on the diketopiperazine function showed a characteristic two proton doublets at δ 3.84 and 4.14 ppm with J_{AB}= 16.6 Hz. In addition, a multiplet at δ 4.00 ppm was assigned to the C-10 methylene protons adjacent to the diketopiperazine ring and the C-8 methine proton. The IR spectrum showed the characteristic absorption bands of C=O stretching of amide at 1667 and 1643 cm^{-1}. The base peak at *m/z* 207 ($[M+H]^+$, 100% relative intensity) revealed by the EI mass spectrum, further confirmed the structure of this molecule.



Scheme 71

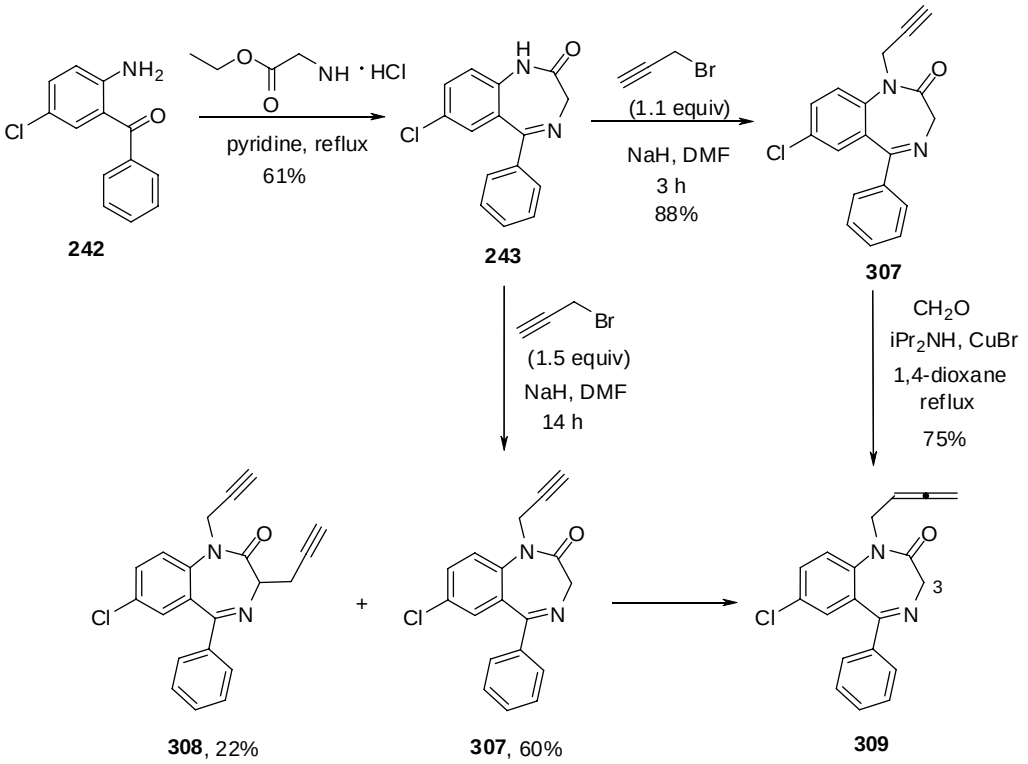
The mechanism of the Crabbé transformation of alkyne **305** to allene **306** involves a cuprous bromide-catalysed Mannich reaction to generate the Mannich base followed by a hydride shift (**343** to **344**) (**Scheme 72**). The hydride in then transferred from the intermediate hydridocopper (III) species (**345**) to C-3 of the allene product. (Searles *et al*, 1984) The presence of Mannich base can be demonstrated by GC monitoring while the hydride rearrangement was proved by deuterium labelling experiments.



Scheme 72

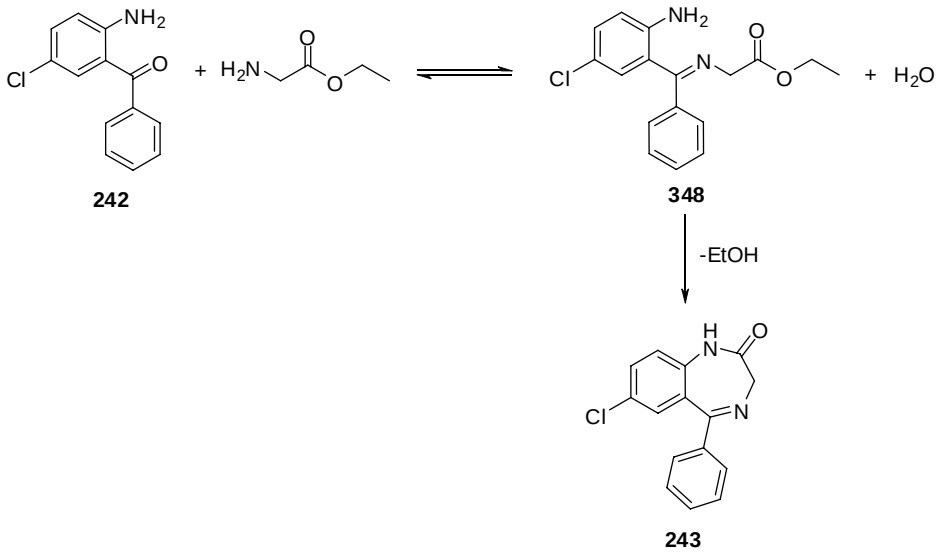
Synthesis of *N*-allenyl -5-phenyl-1,4-benzodiazepin-2-one derivative (309)

The synthesis of 5-phenyl-1,4-benzodiazepin-2-one scaffold (**309**) is shown in **Scheme 73**. 2-Amino-5-chlorobenzophenone (**242**) was reacted with glycine ethyl ester hydrochloride, in pyridine which functioned as both base and solvent, under reflux to afford the bicyclic product (**243**) in moderate yield (61%). *N*-Propargylation of **243** using propargyl bromide (1.1 equiv) and sodium hydride yielded the desired product (**307**) in good yield (88%). When 1.5 equivalent of propargyl bromide was used in the reaction, dipropargylated product (**308**) was also obtained in 22% yield. This compound can be used to generate the di-substituted allene for further study. The Crabbé reaction was used to convert **307** to the desired substituted allenyl product (**309**) in 75% yield. The ^{1}H NMR (400 MHz) spectrum of **309** in $CDCl_3$ showed a multiplet signal at δ 5.25 ppm characteristic of the methine proton of the allene moiety and the two proton methylene signal of the allene gave a multiplet at δ 4.76 ppm. The C-3 methylene protons of the benzodiazepine ring showed a characteristic two protons AB doublet at δ 3.78 and 4.83 ppm with J_{AB}= 10.5 Hz. Additionally, multiplet at 4.47 ppm was assigned to the *N*-methylene protons adjacent to benzodiazepine ring. The IR spectrum showed the characteristic absorption bands of C=O stretching of the amide at 1682 cm^{-1}. The base peak at *m/z* 323 ([M+H]$^+$, 100% relative intensity), revealed in the EI mass spectrum, further confirmed the structure of this molecule.



Scheme 73

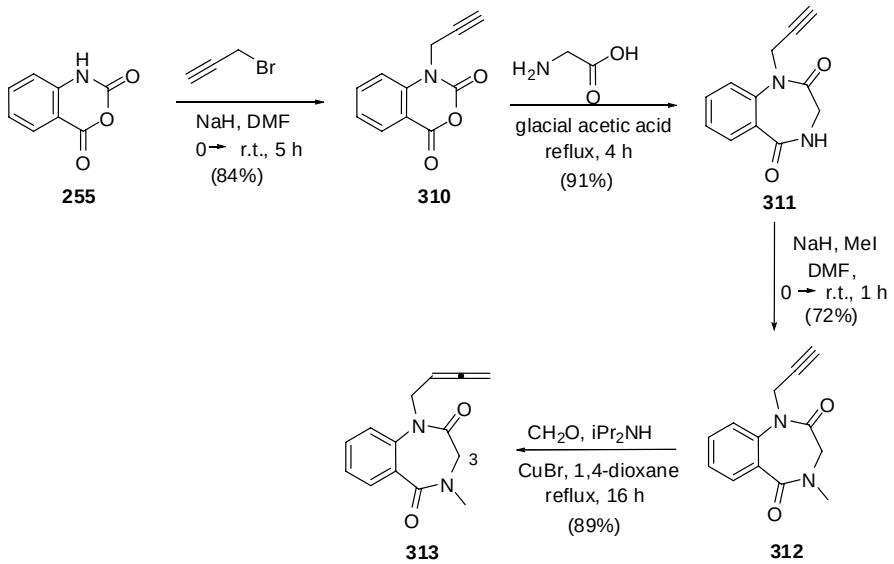
The formation of benzodiazepine **243** only proceeded to 52% conversion. The problem may be due to the formation of water in the process. Water is a side product from the reaction as shown in **Scheme 74**.



Scheme 74

Synthesis of *N*-allenyl-1,4-benzodiazepin-2,5-dione derivative (313)

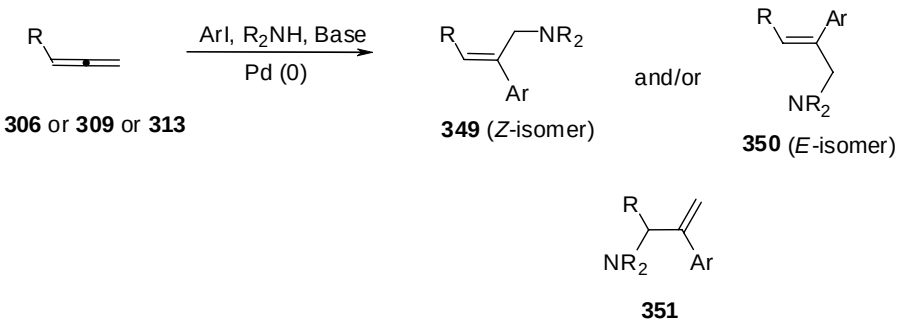
Another scaffold, *N*-allenyl-1,4-benzodiazepin-2,5-dione (**313**), was prepared as shown in **Scheme 75**. Firstly, isatoic anhydride (**255**) was used to generate *N*-propargyl isatoic anhydride by treatment with NaH and propargyl bromide in DMF and the desired product (**310**) was obtained in 84% yield. The resulting product was then reacted with glycine under reflux in glacial acetic acid to yield *N*-propargyl-1,4-benzodiazepin-2,5-dione (**311**) in 91% yield. *N*-Methylation of **311** with NaH and MeI afforded **312** in 72% yield. Finally, the Crabbé reaction was used to produce the substituted allenyl product (**313**) in 89% yield. The ^{1}H NMR (400 MHz) spectrum of this compound in $CDCl_3$ showed a multiplet signal at δ 5.31 ppm characteristic of the methine proton of the allene moiety and the two proton terminal methylene signal of the allene part gave a multiplet at δ 4.82 ppm. The C-3 methylene protons showed a characteristic doublet at δ 3.67 and 4.08 ppm with J_{AB}= 14.5 Hz. In addition, multiplet at 4.37 ppm was assigned to the *N*-methylene protons adjacent to the benzodiazepine ring. The IR spectrum showed characteristic absorption bands of C=O stretching of amide at 1678 and 1646 cm^{-1}. The base peak at *m/z* 243 ([M+H]$^{+}$, 100% relative intensity), shown in the EI mass spectrum, further confirmed the structure of this molecule.



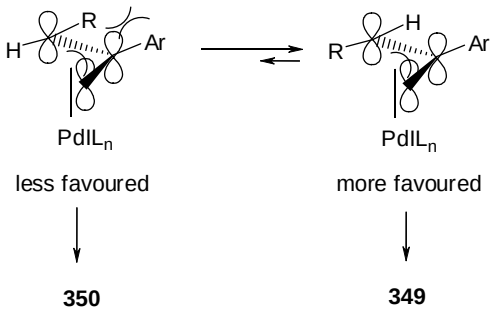
Scheme 75

Three-Component Palladium-Catalysed Cascade Reactions

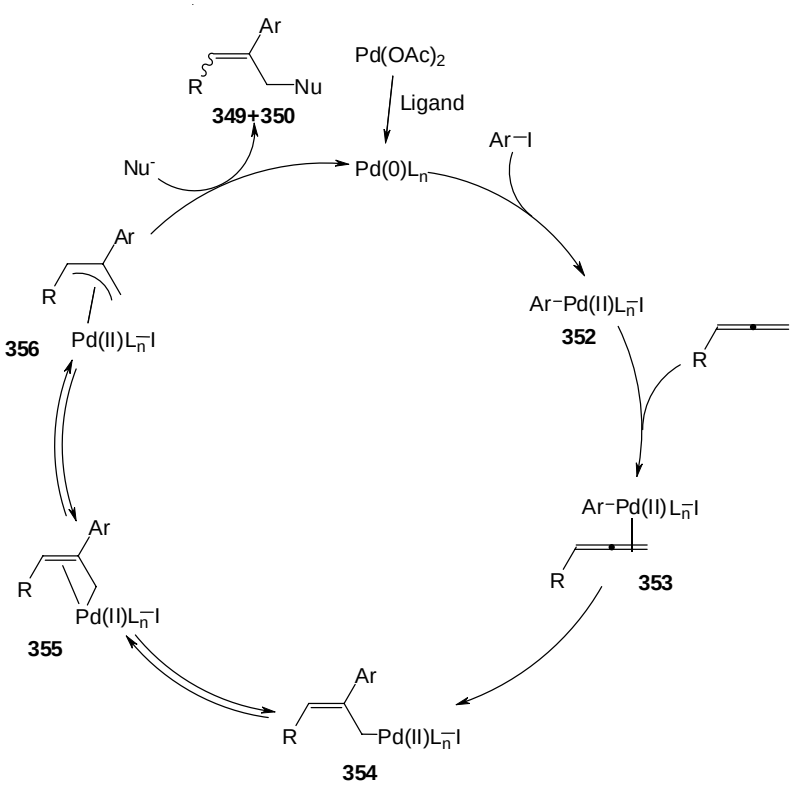
The *N*-allenyl derivatives (**306**, **309** and **313**) were used in the three-component Pd-mediated cascade reaction. The selectivity and mechanism of the processes are shown in **Schemes 76, 77** and **78**. There are three possible outcomes of the reaction (**Scheme 76**). Normally, only **349** and **350** are formed via formation of a π-allyl Pd complex and **349** (*Z*-isomer) is more favoured than product **350** (*E*-isomer) because of less steric hindrance (**Scheme 77**).



Scheme 76



Scheme 77



Scheme 78

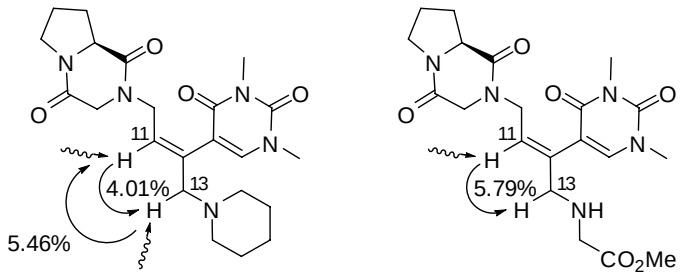
$Pd(OAc)_2/R_3P$ was used as a precatalyst combination. The conversion of $Pd(OAc)_2$ to Pd(0), the active catalyst, employs phosphine ligands as the reductant. (Ozawa *et al*., 1992) The process proceeds by oxidative addition of aryl iodide and Pd(0), π-complex formation of the allene with the aryl-Pd complex and *cis*-insertion of the allenyl moiety to give the σ-complex **354**. Interconversion of σ- and π-allyl palladium complexes can then occur. Nucleophile attack at the terminal carbon of π-allyl palladium complex (less steric hindrance), followed by reductive elimination gives the product and regenerates Pd(0).

Modification of the cascade reaction was achieved by variation of the phosphine ligand, solvent, base and reaction temperature. The general condition used for this process was 1.0 mol equiv. of *N*-allenyl derivative, 1.05 mol equiv. of aryl iodide, 1.2 mol equiv. of nucleophile, 2.0 mol equiv. of cesium carbonate, 10 mol% of

$Pd(OAc)_2$ and 20 mol% of phosphine ligand (tri-2-furylphosphine or triphenylphosphine) in acetonitrile at 60 ^oC.

The results of the cascade reactions are shown in **Tables 8-10** (pages 254-257). ^1H NMR (400 MHz) spectra of the *Z*-isomer of diketopiperazine derivatives (**320**-**330**), 5-phenyl-1,4-benzodiazepin-2-one derivatives (**331**-**335**) and 5-phenyl-1,4-benzodiazepin-2,5-dione derivatives (**336**-**341**) in $CDCl_3$ showed a characteristic signal of the olefinic methine proton of the allene moiety as a triplet in the region of δ 5.70-5.95 ppm, 5.75-5.85 ppm and 5.85-6.07 ppm, respectively.

Most of the three-component products (**320**-**341**) were obtained in moderate to good yield and with high selectivity for the *Z*-isomer, with the exception of the diketopiperazine derivatives **322**, **325** and **328**, when 5-iodo-1,3-dimethyluracil was used in the process (**Table 8**, entries 3, 6 and 9, pages 254-255). In these cases the *E*-isomers were the more favoured products and this was confirmed by NOE experiments (**Figure 9**). When the C-11 proton was irradiated enhancement of the signal of the C-13 proton was observed (4.01% in **322** and 5.79% in **328**). Irradiation of the C-11 proton of *Z*-isomers would not enhance the signal of the C-13 proton.

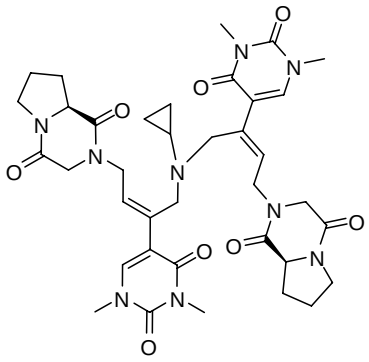


322 **328**

Figure 9. NOE experiments of *E*-isomer of compounds **322** and **328**

The cascade reactions of *N*-allenyl diketopiperazine (**306**) with 5-iodo-1,3-dimethyl uracil and glycine methyl ester as well as that of the *N*-allenyl diketopiperazine **306** with 5-iodo-1,3-dimethyl uracil and cyclopropylamine provided

complex mixture products (^{1}H-NMR). Therefore, the optimisation of these reactions was studied (**Tables 11** and **12**, pages 258-259). In the optimisation for **328**, the use of ($Pd(PPh_3)_4$) resulted in only two isomers (entries 13-17, **Table 11**, page 258) with entry 17 (**Table 11**) giving the best conditions to synthesize **328**. Whereas the attempted optimisation of **325** the best conditions which the ^{1}H-NMR spectral data showed one or two isomers could not be found (**Table 12**, page 259). Thus, one condition was chosen for the synthesis which was *N*-allenyl diketopiperazine (**306**, 1.0 mol equiv), 5-iodo-1,3-dimethyl uracil (1.05 mol equiv), cyclopropylamine (1.2 mol equiv), Cs_2CO_3 (2.0 mol equiv), 10 mol% of $Pd(OAc)_2$, 20 mol% of trifurylphosphine ligand in acetonitrile (entry 1, **Table 12**). The ^{1}H-NMR spectrum of the crude residue seemed to reveal two isomers. The ^{1}H-NMR spectrum of the purified products in $CDCl_3$ showed three triplets in the region of the olefinic proton. When the solvent was changed to C_6D_6, the ^{1}H-NMR spectrum showed four triplets while the ^{1}H-NMR spectrum in C_6D_6 at 70 ^{o}C still showed four triplets. The mass spectral data showed the base peak at *m/z* 746 which indicated that it is the molecular ion peak of the dimer product (**357**)(**Figure 10**). This dimer was formed by attack of the secondary amine of the predicted 3-component product (**325**) to the other π-allyl palladium complex.



357

Figure 10. Dimer (**357**) from the cascade reaction of *N*-allenyldiketopiperazine using 5-iodo-1,3-dimethyl uracil and cyclopropylamine

The cascade reactions of *N*-allenyl diketopiperazine with various nucleophile was studied. When glycine methyl ester was used as nucleophile (entries 7-10, **Table 8**, page 254), the rate of reaction was slower than with other nucleophiles because of the lower pKa of the amine moiety in glycine unit. This requires the reaction to be conducted at higher temperature for a longer time. Comparing secondary amines (morpholine and piperidine) and primary amines (glycine methyl ester), the rate of reaction of the secondary amines was faster than that of the glycine ester because of greater nucleophilicity of the secondary amines (**Table 8**).

The 1,4-benzodiazepine and diketopiperazine cascades gave the *Z*-isomer as the major or sole product except when 5-iodo-1,3-dimethyl uracil was used with the diketopiperazine, the *E*-isomer was the major product (entries 3, 6 and 9, **Table 8**). In the syntheses of 1,4-benzodiazepine derivatives, the primary amine (cyclopropylamine) was less reactive than secondary amine (*N*-methylpiperazine) (entries 1 and 3, **Table 9**, page 256).

CONCLUSION

In this work, the three-component Pd-catalysed cascade reaction utilizes *N*-substituted allene, aryl iodide and nucleophile, and with Pd(0) as catalyst. *N*-Substituted allenes used in the cascade reaction are *N*-allenyl diketopiperazine (**306**), *N*-allenyl-5-phenyl-1,4-benzodiazepin-2-one (**309**) and *N*-allenyl-1,4-benzodiazepin-2,5-dione derivatives (**313**). These substituted allenes were prepared from *N*-propargyl products (**305**, **307** and **312**) by the Crabbé reaction.

N-Allenyl diketopiperazine (**306**) was synthesized in three steps from *L*-proline methyl ester hydrochloride (**304**) *via* acylation, diketopiperazine ring formation and the Crabbé reaction. Synthesis of *N*-Allenyl-5-phenyl-1,4-benzodiazepin-2-one (**309**) was achieved in three steps starting from 2-amino-5-chlorobenzophenone (**242**) with an overall yield of 61%. The reactions involved amidation and condensation, propargylation and the Crabbé reaction. *N*-Allenyl-1,4-benzodiazepin-2,5-dione derivative (**313**) was prepared in four steps from isatoic anhydride (**255**) *via* propagylation, condensation, methylation and the Crabbé reaction with an overall yield of 49%.

Eleven diketopiperazine, five 5-phenyl-1,4-benzodiazepin-2-one and six 1,4-benzodiazepin-2,5-dione derivatives were synthesized in moderate to high yield with high regioselectivity from this process. Exception of the reaction of *N*-allenyl diketopiperazine derivative (**306**) with 5-iodo-1,3-dimethyluracil, the reactions had no selectivity and provided the *E*-isomer as the major products. In the case of the nucleophile, the reaction rate, when using secondary amine, was faster than that of the primary amine because of better nucleophilic character.

The three-component palladium-catalysed cascade reaction can generate complex heterocycles containing a tri-substituted double bond in one step with moderate to good yield. The complex heterocycles were formed by two new bonds with predictable regiochemistry. The regioselectivity and rate of reaction depend on

the nature of substituted allene, nucleophile, phosphine ligand, solvent, base and/or temperature. Moreover, the application of these cascade reactions has potential to rapidly produce a wide variety of compounds which could possess improved biological characteristics. This cascade process is also more convenient, effective and less wasteful.

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